SYPHILIS

ITS COURSE AND MANAGEMENT

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FOREWORD

WITHIN the span of two world wars many advances in scientific and medical fields have been recorded. With respect to the venereal diseases, the advances have been most striking As a result of antibiotic therapy gonorrhea, the most prevalent infection of the group, has almost passed from the scene as an important clinical and public health entity Syphilis, because of its chronicity will require a greater lapse of time for a complete evaluation of the effectiveness of modern therapy

In view of the results already obtained with penicillin therapy syphilis is changing in its public health importance and in its capacity to injure human beings. Doctor Thomas, as an observer of events which are still in the process of unfolding has caught the transition and presents the trends which are now becoming apparent. He brings to the work a keen clinical ability a broad experience, a sound analytical capacity and a thoughtful perspective.

The book presents a concise review of the status of syphilis today It should be of the greatest help to the general medical man as an authentic presentation of the situation existing after ten years of intensive therapy and after five years of antibiotic therapy The student as well as the specialist should find the volume a useful guide in a complicated field of medicine.

It is hoped that upon the present volume Doctor Thomas will build a series of revisions which will carry the disease through the period of change and which will attempt a final evaluation of the events now taking place.

JOHN F MAHONEY M.D

ACKNOWLEDGMENTS

ALTHOUGH I alone am responsible for the choice of the material presented in this book and for opinions on controversial points, I was greatly aided in writing the manuscript by Dr William Leifer of the Department of Dermatology and Syphilology at Bellevue Hospital. Doctor Leifer has had wide experience with syphilis in both civilian life and the Army He generously gave much time to reading and editing each chapter of this book. I am indebted to him for many editorial changes. I am also grateful to Dr John F Mahoney and Dr Charles R. Rein, who read the manuscript with critical care and to my wife, Ruth B Thomas, who gave me valuable suggestions.

For the material included in the book, I am indebted to many colleagues both at Bellevue Hospital and elsewhere. I cannot mention all by name, but I am especially indebted to Drs. Gertrude Wexler Simeon Landy Bernhard Dattner Gerald Flaum, Mortimer D Speiser and Max Schur who have worked with me at Bellevue Hospital. When we first started the rapid treatment of early syphilis late in 1939 Dr Wexler was largely responsible for inaugurating a system of record keeping which has been of continuing value in making information readily available. The effects of her conscientious and able work during the years 1938 to 1945 are still felt on our service. Since her departure from Bellevue Hospital, Dr Landy has carried on many of Dr Wexler's former services with exceptional thoroughness and care. The high quality of Dr Dattner's work in neurosyphilis is well known, and I am indebted to him not only for his careful research and records but also for numerous suggestions in preparing the chapter on neurosyphilis. Doctor Flaum has been an attending physician on our service since his discharge from the Navy in 1945 He is now engaged in a long-term study of cardiovascular syphilis, and he assisted Dr Speiser of the Department of Gynecology and Obstetrics, in collecting and preparing data on the results of penicillin therapy of syphilis associated with pregnancy and the follow up of babies delivered by treated mothers. I am indebted to Dr Flaum for his assistance in preparing the chapter on cardiovascular syphilis and for his reading of the manuscript of the entire book. Doctor Speiser made valuable suggestions in the preparation of the chapter on syphilis and pregnancy To Dr Ber

nard I Kaplan I am indebted for much of the material presented in the chapter on late latent syphilis. The charts in that section were all provided by Dr Kaplan, and I am grateful to him for his careful review of the entire chapter

The data on the penicillin treatment of syphilis now available at Bellevue Hospital could not have been collected without the financial assistance of the United States Public Health Service and the Office of Scientific Research and Development (during World War II) I am greatly *indebted to the public health nurses, investigators, and office staff at the* Rapid Treatment Center at Bellevue Hospital for their interest and faithfulness in keeping patients under observation and preserving accurate records. To the clinic and ward nurses I also express my gratitude not only for their care of the patients but also for their attitude which has helped to keep patients under observation for long periods. Special mention should be made of Miss Lena Taucci whose services as treatment nurse in the syphilis wards of Bellevue Hospital have been of great value not only in the management of patients but also in the organization of the service, and of Miss Esther Higgins, charge nurse of the syphilis clinic in the Out Patient Department.

The chapter on the public health aspects of syphilis, contributed by Dr Theodore J Bauer adds much to this book, and I am grateful to him and to the Venereal Disease Division of the United States Public Health Service and New York State Department of Health and the Bureau of Social Hygiene of New York City Department of Health for their co-operation. I also wish to acknowledge with much gratitude the interest and help of Dr Joseph Earle Moore during the years following my original training in syphilis on his service at Johns Hopkins Hospital. Although I have not burdened Dr Moore with reading the manuscript of this book, I am indebted to him for past help in making the book possible.

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INTRODUCTION

Recent advances in laboratory tests for syphilis and the discovery by Dr John Mahoney and his coworkers that penicillin is an effective anti syphilitic agent have so revolutionized the management of syphilis that there is room for a new book on the subject. This book, however does not pretend to be a complete text on syphilis. Excellent textbooks which give detailed portrayals of the many manifestations of syphilis already exist. It would indeed be difficult to improve on the description of syphilitic signs and symptoms made by Fournier in France during the early part of this century and more recently by Stokes in this country My purpose is not to add to the already voluminous literature describing syphilis but to provide as much understanding of the various stages of the disease as our present knowledge permits and to outline principles of treatment.

To accomplish this purpose I have stressed the immunology of the disease, the course of untreated syphilis, the interpretation of laboratory procedures on which we are largely dependent for diagnosis, and the modern treatment of the various stages of the infection, based, for the most part, on our experience with penicillin therapy at Bellevue Hospital in New York City

Few diseases are so complex and secretive in their mode of action as syphilis. The more one sees of its protean manifestations, the more one is aware of its tendency to surprise and confound even the trained observer The isolated manifestations of syphilis are certain to be misdiagnosed or mistreated on occasions, unless we understand the disease as a whole. And, in spite of the progress made during the past years, it is disconcerting to find how much we know about some aspects of the infection yet how little the disease as a whole is understood. That this is true is not surprising, partly because specialists are likely to encounter syphilis only as it produces manifestations which fall under their specialty A neurologist may be skilled in recognizing the signs of neurosyphilis yet be indifferent about such questions as whether the syphilitic process is active or inactive and how much and what kind of antisyphilitic treatment should be given, if any Much the same can be true of cardiologists, ophthalmologists, orthopedists, etc., whose knowledge of syphilis is confined largely to their own specialties. Even the expert syphilologist is hard put to answer many ques-

tions which arise in the diagnosis and treatment of syphilis because our understanding of the disease is limited by our lack of knowledge regarding the virulence of the invading microorganisms and the immune reactions of the host. But, in spite of our ignorance of the exact manner in which syphilis acts and why certain phenomena occur we now have at our disposal more effective means of diagnosing and treating the infection than ever before.

True, perplexing problems of diagnosis still exist. Until serologists can differentiate accurately between true positive serologic tests for syphilis and biologic false tests, the physician can do no more than hazard a guess, at times, as to whether or not a patient actually has or has ever had the disease but such cases are exceptions to the rule. Much less unusual are problems of determining the activity of a syphilitic infection and deciding the need for treatment. The all too common practice of treating every patient with positive serologic tests for syphilis until the tests become negative cannot be too strongly condemned. Many patients in past years undoubtedly have been overtreated for syphilis, with potentially toxic drugs, because of a desire to obtain negative serologic tests.

The introduction of quantitative tests for syphilitic reagin (antibody) in the blood serum has not solved the problem of determining the activity of a syphilitic infection in all cases, but such tests are valuable aids in the follow-up of treated patients. In fact, they are so helpful that one now wonders why they were not generally adopted long ago. In themselves they do not necessarily establish the diagnosis of syphilis. They must always be interpreted in the light of the history and physical findings of the patient. Thorough histories as well as thorough physical examinations are essential for differential diagnosis, but without the aid of laboratory tests we would often be led astray

For the management of syphilis, quantitative serologic tests of both the blood and spinal fluid are so important that I have devoted considerable space in this book to summarizing our experience with them at Bellevue Hospital. Through the interest and assistance of Dr Augustus B. Wadsworth, who recently retired as Director of the New York State Department of Health laboratories, quantitative complement fixation tests for syphilis were in routine use at Bellevue Hospital some years before they became available generally We have been fortunate in being able to work in close co-operation with the New York City Branch of the State Department of Health laboratory for the past nine years. Few serologic laboratories have been more progressive and exacting in their work than those of the New York State Department of Health The staff of the central

laboratory has constantly improved the techniques for tests of both blood serum and spinal fluid. Members of this staff were the first to introduce quantitative complement fixation tests for syphilis reported in units in both blood serum and spinal fluid, and the first to introduce and use cardiolipin antigen. Doctor Carl Lange, who has been with the laboratory for many years, has improved his original colloidal gold test so that it now yields more consistent results and provides quantitative as well as qualitative information.

I am indebted to Dr Gilbert Dalldorf the present director of the New York State Department of Health laboratory for continuing the co-opera tion started by Dr Wadsworth, and to Dr Edgar R. Maillard, who is in charge of the branch laboratory in New York City

In addition to the co-operation of the New York State Department of Health laboratory we have had the exceptionally able assistance of the Venereal Disease Research Laboratory of the United States Public Health Service at the Marine Hospital, Staten Island. Under the direction of the V.D.R.L., a laboratory was established at Bellevue Hospital for routine quantitative Kahn tests. More recently Dr Charles R. Rein, formerly Chief of the Division of Serology Army Medical School, has joined our staff Thus, we have had the advantage of the highest grade of laboratory assistance in our work.

In this book the treatment of syphilis is confined largely to the use of penicillin. In past years the routine therapy of syphilis consisted chiefly of alternate courses of weekly injections of heavy metals and arsenical drugs. Schedules of therapy for the various classifications of syphilis were carefully worked out and, when followed by physicians and patients, proved reasonably effective, except in the treatment of neurosyphilis. Unfortunately however from one to two years of regular weekly injections were required by these schedules. Only some 5 to 20 per cent of clinic patients reported regularly for the required amount of treatment. Every time that therapy was omitted, the infecting microorganisms benefited. As a result, physicians in charge of antisyphilitic therapy were constantly balked in their efforts to complete the treatment of most clinic patients. One never knew when it was safe to stop treatment for patients who received irregular injections. Many patients were continued on such irregular treatment for years, and many more were lost entirely before they had received ade quate therapy Although in late syphilis even a little treatment may assist the body to establish greater resistance to the infection, in early syphilis the reverse is usually true. Therefore, rapid treatment of early syphilis was urgently needed

Various modifications of the massive arsenotherapy for early syphilis, first used by Hyman Chargin, and Leifer were beginning to fill this need prior to the advent of penicillin. The intensive use of arsenical drugs is always associated with serious risk in a small percentage of individuals, but the incidence of serious reactions was being lowered before penicillin made the more dangerous massive arsenotherapy unnecessary

At Bellevue Hospital rapid treatment of early syphilis was started in December 1939 By the addition of four fevers induced by typhoid vaccine, the dosage of arsenoxide needed for the rapid treatment of early syphilis in ten days was cut in half with a resulting lowered incidence of serious reactions. Nevertheless, in spite of many precautions, one death from arsenical encephalopathy occurred among more than 2 000 patients treated with fevers and arsenoxide. This fatality represented a marked reduction from the 0.3 per cent resulting from intensive treatment with arsenoxide alone, and, in view of the rare fatal reactions caused by arsenical encephalopathy even when the drugs were given by weekly injections, we believed that the advantages of rapid therapy justified its use. I still recall, however the anxiety with which we observed reactions to arsenical drugs among our patients in the prepenicillin era. Therefore, unless arsenical drugs can be used cautiously I see no reason for using them at all except in cases when syphilitic lesions may fail to respond to penicillin

Penicillin therapy for syphilis at Bellevue Hospital was made possible largely through the assistance of the United States Public Health Service and the Subcommittee on Venereal Diseases of the National Research Council. In April, 1943 under the sponsorship of the United States Public Health Service, the New York City Department of Health, and the New York City Department of Hospitals, a Rapid Treatment Center was established at Bellevue Hospital. In November 1943 we started the rapid treatment of early syphilis with penicillin, provided through the Subcommittee on Venereal Diseases of the National Research Council. This committee, in the fall of 1943 initiated a large-scale investigation of penicillin therapy for syphilis in a number of institutions throughout the country The follow-up reports on patients treated with a variety of schedules of penicillin were pooled in a Central Statistical Unit under the direction of Dr Joseph Earle Moore at Johns Hopkins Hospital. The investigations started by the Subcommittee on Venereal Diseases of the National Research Council have recently been carried on by a similar Committee of the National Institute of Health of the United States Public Health Service.

The results of the various studies sponsored by the above committees

should prove of great value. But early in 1948 when the material for this book was prepared, reports of the data accumulated by the Central Statistical Unit were not up to date, and the number of cases involved was so great that an immense amount of detailed analysis was required before the statistics could be properly evaluated.

At the Rapid Treatment Center at Bellevue Hospital we had treated over 12,000 cases of syphilis with various schedules of penicillin therapy when the material for this book was analyzed. Only about half of the penicillin-treated patients were placed on a research basis for intensive follow-up studies, but the material available to us has been so great that it affords ample evidence for the conclusions reached.

Unless the Treponema pallidum develops increased resistance to penicillin, an eventuality which at present seems unlikely there can be no doubt that penicillin should supplant arsenical drugs in the treatment of syphilis. All types of syphilis can now be treated more effectively with penicillin in a few weeks than with the older forms of therapy requiring weekly injections for one to two years. I do not pretend to be able to give optimum schedules of penicillin therapy for syphilis at this time. For the present, and probably for some time to come, physicians will have to choose from a variety of suggested treatment schedules for syphilis. Penicillin can be used in various combinations with heavy metals, arsenical drugs, and fever but so far in most cases, penicillin has proved as effective alone as in combination with other agents. More time must pass before optimum plans of treatment can be determined, but we already have sufficient data to justify relatively rapid treatment of all types of syphilis with penicillin.

Because penicillin has proved so effective, I have given less space to descriptions of the various bismuth and arsenical preparations than would otherwise have been necessary In an endeavor to be brief I may have been guilty of unfortunate omissions and of a certain amount of dogmatism. I hope the reader will find no misstatement of fact. Correction of any errors of this kind will be welcome. Legitimate differences of opinion regarding some of my conclusions may well exist. In such cases the interested reader must seek the opinion of other syphilologists and come to his own conclusions. One of my purposes is to stimulate thought and further investigation, but, in the main, I have written to give busy individuals a practical understanding of the principles underlying the modern diagnosis and treatment of syphilis.

CHAPTER 1

ETIOLOGY OF SYPHILIS

The etiologic agent of syphilis is a corkscrew-shaped microorganism known as the Spirocheta pallida or Treponema pallidum (plural Treponemata pallida) The term Spirocheta is used for a variety of macroscopic and microscopic organisms and was first applied by Ehrenberg in 1838 only to large, free-living forms. Since Ehrenberg's introduction of the term, Spirocheta have been classified into numerous subdivisions, of which treponemes are one. According to Zinsser and Bayne Jones, treponemes, of which T pallidum is only one variety are more closely related to bacteria than to protozoa.

Morphology.—Treponema pallidum has a cylindrical, corkscrew shaped body with 8 to 14 regular rigid spirals. In the living state the spirals change only slightly although the body may undulate or occasionally bend at right angles.

Identification.—Treponema pallidum is best visualized by dark field illumination. With the aid of a dark-field microscope it can be identified with accuracy by experienced observers. When examining serum from human lesions, T pallidum must be differentiated from T refringens, T microdentium, and T macrodentium. Treponema refringens is frequently found in genital lesions, but it is easily differentiated from T pallidum by observing it in motion. Treponema refringens is less delicate than T pallidum the spirals are less rigid, changing markedly during movement. Treponema microdentium has a morphology almost identical with that of T pallidum. In my experience, however T microdentium and T macrodentium are found in the mouths of human beings only at the margins of the gums or beneath the gums. I have not found them elsewhere in the mouth. Also, in my experience, lesions of the lips, buccal mucous membranes, tongue, or throat which contain treponemes with the typical morphology of T pallidum have always been syphilitic. Consequently in cases of probable syphilis I do not hesitate to make the diagnosis of early syphilis when treponemes with the morphology of T pallidum are found in lesions of the mucous membranes of the mouth, with

the exception of the gums. In such cases, however the diagnosis should always be checked by careful histories and serologic tests for syphilis. Treponema pallidum is stained with difficulty and stained smears are an unreliable means of identifying it because its characteristic appearance is lost when dried and stained. In tissue sections T pallidum can be demonstrated by means of silver impregnation techniques.

Resistance.—Outside the body T pallidum dies rapidly It is killed by drying and is quickly destroyed by soap and water Inside the human body the microorganism is unusually resistant to the protective mechanisms of the body High body temperatures will kill T pallidum, but it is improbable that the treponemes are destroyed by temperatures which are tolerated by human beings. Other mechanisms than the temperature alone probably contribute to the value of fever therapy for syphilis. According to Boak, Carpenter and Warren, testicular emulsions containing T pallida are rendered noninfectious by an exposure of 5 hours at 39 C, 3 hours at 40 C, 2 hours at 41 C and 1 hour at 41.5 C. At ordinary temperatures outside of the body T pallida will survive in tissues and blood for varying periods up to 3 to 4 days. I have found motile treponemes in early syphilitic lesions of cadavers kept in an icebox for 48 hours.

Cultures.—Cultures of virulent T pallidum have not been grown Noguchi in 1912 believed that he had cultured virulent T pallida, but his experiments have not been confirmed. Treponemes have been cultivated in artificial media by numerous investigators, but they have been avirulent. Cultures of an avirulent treponeme, known as the Reiter strain are available for experimental purposes at the present time.

Habitat.—Normally T pallida are found only in human beings. Monkeys, rabbits, and South American llamas develop syphilitic lesions when inoculated with virulent treponemes. When injected into rats, mice, and guinea pigs, T pallida live as harmless parasites without causing lesions. The rabbit is usually employed for experimentation

Nichols strain.—The Nichols strain of T pallidum was originally isolated from the spinal fluid of a human being with syphilis and was injected into rabbits. It has been preserved for over 20 years by the inoculation of new generations of rabbits *and has lost none of its original virulence*. The Nichols strain is now used in many parts of the world for experimentation in syphilis.

Life cycle.—Levaditi and others have suggested that T pallidum has a life cycle with resting granular forms. The evidence for this suggestion

has so far been unconvincing, but further investigation of the life history of T pallidum is needed.

Variations in strains.—Largely because of the failure to culture virulent T pallida, we know nothing as yet about the variety of strains which may exist. We do not know whether or not the treponemes causing syphilis vary in virulence, nor do we have any scientific evidence that certain strains of T pallidum have a special affinity for special tissues, such as the central nervous system in human beings.

The need for further investigations of T pallidum is great. Since virulent treponemes have not been cultured on artificial media, further knowledge about possible variations in virulence might be gained by inoculating rabbits with infected material from a variety of lesions in different human beings. The isolated strains could be preserved in the same manner as the Nichols strain Years of observation of the many possibly different strains of treponemes inoculated into rabbits might add to our knowledge of variation in virulence.

REFERENCES

Beerman A. "Functional Variations of Treponema Pallidum," *Am. J Syph., Gonor & Ven. Dis.* 22 301 1938.

——— Van Haelst J and De Wilde, H. An Experimental Study of the Problem of the Existence of an Invisible Form of the Syphilitic Virus, and of Spontaneous Spirochetosis in Rabbits," *Am. J Syph. & Neurol.*, 19 161 1935

Boak, H. A. Carpenter, C. M. and Warren S L. "Studies on Physiological Effects of Fever Temperatures, *J Exper Med.*, 56 741 1932.

Wile, U J "Transmission of Experimental Syphilis from Mouse to Mouse —Absence of Spirocheta Pallida and of Pathologic Changes in Presence of Successful Inoculation," *Am. J Syph. G nor & Ven. Dis.*, 31 109 1947

Zinsser H., and Bayne Jones S.: *T xtbook of Bacteriology* 8th ed., D Appleton-Century New York, 1939

CHAPTER 2

A GENERAL DESCRIPTION OF THE COURSE OF UNTREATED SYPHILIS

In order to appreciate and evaluate the influence of treatment in syphilis, one must first understand the variable course of untreated syphilitic infections.

MODE OF INFECTION

Because T pallida dwell habitually only in human beings and cannot thrive outside of the body syphilis is almost always contracted by the direct transference of the microorganisms from one person to another The contact of moist surfaces is necessary for infection. Usually the infection is transmitted by sexual contact.

Infections have occurred through contact with mucous or serous secretions containing treponemes. I once found T pallida in a chancre on the shoulder of a man over 80 years of age. He acquired the infection from a young infant with congenital syphilis by carrying the baby with its head on his bare shoulder He was undoubtedly infected by the mucous discharges from the baby's mouth and nose. Such instances are extremely rare. If syphilis were as infectious by ordinary contact as many people think, most of the population would be infected. It is improbable that syphilis is spread to any appreciable extent by drinking glasses and eating utensils. Moist towels might be infectious if used immediately after being rubbed over the moist sores of early syphilis, but there is no evidence that many infections are caused in this manner Nevertheless, in spite of the fact that syphilis is usually acquired by intimate contact with the moist surfaces of an infected individual, everyone with early lesions should be cautious about using towels and drinking vessels used by others.

LOCAL PROPHYLAXIS

To acquire syphilis, infectious material must not only be transferred to the surface of the skin or mucous membranes, but the treponemes must also penetrate into the subjacent tissues. Once the microorganisms have

penetrated the mucous membrane or skin it is doubtful that local prophylactic measures are of much value. Efficient local prophylaxis aims at preventing the entrance of treponemes into the body Washing with soap and water immediately after contact probably has more value than any chemical application used an hour or more after exposure. Mechanical prophylaxis with a condom can be effective but does not always prevent infection.

ASYMPTOMATIC PERIOD OF EARLY SYPHILIS

After the T pallida have entered the body they begin to multiply The rate at which they increase numerically depends on the number of treponemes originally invading the body and on other indeterminate factors such as the resistance of the host and possibly the kind of tissue infected.

Rate of increase of treponemes after infection.—Magnuson, Eagle, and Fleischman found that "on intracutaneous inoculation of rabbits, the incubation period of the primary lesion of syphilis varied linearly with the size of the inoculum over a range of 2 to 200 000 treponemes with an average increment of four days for each ten-fold decrease in the number of treponemes inoculated." * Assuming that each microorganism divides into two, the authors conclude from their experiments that each treponeme probably divides once in about every 30 hours. This estimate of the rate at which treponemes divide in rabbits does not take into account possible variations in the resistance of the host, nor is it offered as a scientifically proved fact, but the evidence for the authors conclusions is based on carefully conducted research. The experiments were done under controlled conditions, and a single known strain of T pallidum (the Nichols strain) was used for the inoculation of rabbits. We know nothing about the possible variations in the strains of the syphilitic virus, but there can be no question that the number of infecting microorganisms is one important factor determining the rate of numerical increase of treponemes in the human body and the length of the incubation period of primary lesions. Other factors, such as the varying virulence of the infecting microorganisms and the resistance of the host, may also significantly affect the rate of increase of treponemes after infection.

Duration of asymptomatic period after infection.—The incubation period of the chancre the primary lesion of syphilis, is said to be between

* Magnuson, H. J Eagle, H.; and Fleischman R. "The Minimal Infectious Inoculum of Spirochaeta Pallida (Nichols Strain) and Consideration of Its Rate of Multiplication in Vivo, *Am. J Syph., Gonor & Ven. Dis* 32 1 1948.

10 and 90 days. Thus, the asymptomatic period of early infection varies widely in duration among individuals who react to the infection with the development of a chancre. Unfortunately however some males and many females apparently acquire syphilis without the development of a visible chancre. Usually the chancre appears in males within 3 or 4 weeks after infection, but less than 50 per cent of infected females have chancres which are observed by either the infected individuals or the examining physicians. Most females react to the generalized infection of syphilis with secondary lesions, but these secondary lesions never appear before the sixth week and in most cases not for 8 to 16 weeks after infection Thus, many women have no observable lesions of early syphilis during the first 2 or 3 months after infection.

Treatment of gonorrhea with penicillin may prolong the asymptomatic early period of syphilis in patients infected with both gonorrhea and syphilis. To rule out syphilis in such patients, repeated physical examinations and serologic tests for syphilis must be made over a period of 6 months.

Incidence of infection without early lesions.—In some cases syphilis is acquired without the appearance of any detectable early lesions, but the frequency of this occurrence is unknown. Histories taken from individuals with late syphilis are of little value in this respect, since many patients forget about their early lesions or deliberately lie about them. In other cases the lesions may have been so insignificant and transient as to pass unnoticed or to be utterly disregarded. That syphilis may be acquired without the appearance of demonstrable lesions for 3 or 4 months after the development of positive serologic tests for syphilis has been proved in my own experience, and in all probability the early stages of syphilis pass unnoticed in from 15 to 30 per cent of infected individuals.

Summary —The asymptomatic period of early syphilis is not synonymous with the incubation period of the chancre. In most males and in less than half of infected females, the early asymptomatic stage represents the period between infection and the appearance of a chancre In a relatively small number of males and a large number of females it represents the period between infection and the appearance of secondary lesions In an unknown percentage of cases it represents the period between infection and the development of late manifestations of syphilis. The diagnosis, however can be made in practically all cases within 4 to 12 weeks after infection by means of positive serologic tests for syphilis.

PRIMARY SYPHILIS

By definition, primary syphilis is the stage of the disease during which

the initial lesion of syphilis (chancre) can be diagnosed. In many cases there is nothing characteristic about a chancre. It may or may not be indurated. It usually begins as a papule which becomes eroded and moist. If T pallida have penetrated the mucous membranes or skin at more than one site, multiple chancres may develop and it is by no means unusual to see multiple primary lesions of syphilis. Apart from the chancre, the only other physical sign of primary syphilis is enlargement of the regional lymph nodes.

Incubation period of primary syphilis.—As previously noted, the incubation period of the chancre is relatively long and varies greatly in different individuals, depending in part, on the number of infecting treponemes. Chancres seldom appear less than 2 weeks or more than 8 weeks after infection The usual time interval is 3 to 4 weeks after infection. As serologic tests for syphilis rarely become positive until at least 4 weeks * after infection, the chancre often appears before the tests of the blood serum are positive. As a result, primary syphilis may be diagnosed in the seronegative phase. The diagnosis is made by demonstrating T pallidum by dark field microscopic examination.

Duration of primary syphilis.—The duration of primary syphilis varies considerably depending on the size of the chancre and the amount of induration present. In all cases, however chancres are self-limited and heal without treatment. The secondary lesions of syphilis generally develop before the chancre disappears, but occasionally the primary lesion heals before secondary manifestations become evident. Thus, the primary and secondary stages of syphilis may overlap or may be separated by variable periods of time.

Infectiousness of blood in primary syphilis.—By the time the chancre has developed, the infected individual already has a blood-stream infection. We do not know how soon after infection treponemes are in the blood of human beings. Undoubtedly the time varies in different individuals, but certainly the treponemes have entered the blood stream before any lesions appear Such evidence as we now have suggests that the appearance of the chancre marks the time when the blood is most infectious. Apparently during the first few weeks of infection the treponemes live and multiply in the blood and lymphatics. The theory is that the tissues at the site of infection are sensitized by the invading treponemes and react with the formation of a chancre only after a pronounced blood-stream infection has developed. But, whether or not this theory is correct,

* With the increase in sensitivity of the newer tests, positive serologic tests for syphilis are found earlier than in former years.

treponemes do not remain long in the blood. During the early part of the primary stage, or before it, the microorganisms leave the blood stream and invade the other tissues of the body This generalized invasion of the body by T pallida usually results in the development of lesions that characterize the secondary stage of syphilis.

SECONDARY SYPHILIS

Secondary syphilis is the designation for that stage of syphilis during which definite, generalized clinical manifestations can be demonstrated. The lesions of secondary syphilis represent the initial reactions of various tissues of the body to T pallida carried to them by the blood and lymphatics. The lesions contain treponemes in large numbers, and their demonstration in skin and mucous-membrane lesions by dark field microscopic examination is diagnostic. This fact, furthermore, is proof of a preceding blood-stream infection. By the time secondary lesions appear the blood-stream infection has greatly diminished, and in all probability the treponemes remain in the blood only long enough to be transferred to other sites in the body This does not mean that the blood during the secondary stage of syphilis is sterile, because treponemes are undoubtedly seeded intermittently into the blood stream from many foci of infection during this stage.

Tissues involved by secondary syphilis and incubation period of lesions.—No doubt all of the tissues in the body are invaded during the early stages of infection, but demonstrable lesions of secondary syphilis do not occur in all tissues. Manifestations of secondary syphilis may develop at many different sites, but the diagnosis is commonly made by the presence of lesions in the skin or mucous membranes. As a rule, the signs and symptoms of secondary syphilis develop anywhere from 2 to 6 months after infection. In rare instances they may not be apparent for more than 6 months after the onset of infection. The reasons for the wide variation in the incubation period of secondary lesions are unknown. As previously noted, the rate of increase and distribution of treponemes after infection varies in different individuals, and it is also possible that the time required for lesions to develop after treponemes lodge in the tissues varies in different individuals. Both of the above factors, as well as unknown immunologic processes, may play a part in determining the length of the incubation period of secondary lesions.

Secondary syphilis in the sexes.—It has been my experience that the clinical manifestations of secondary syphilis are no less common in females than in males. It is true, however that over many years secondary

syphilis has been diagnosed more frequently in males than in females. Some of the discrepancy in statistics as to the relative incidence of secondary lesions in the two sexes may be due to the fact that small genital lesions are more conspicuous in males than in females. Certainly the manifestations of secondary syphilis do not differ appreciably in the sexes.

Variations in the severity of secondary manifestations.—No attempt will be made in this chapter to describe the various secondary manifestations that may occur. As with primary syphilis, secondary syphilis should not be diagnosed by the clinical manifestations alone; the diagnosis must always be confirmed by dark-field demonstration of T. pallida and by positive serologic tests for syphilis. Not only are the signs and symptoms of secondary syphilis diverse, but they differ greatly in intensity. The suggestion has been made that the more extensive and pronounced the reaction of the skin during secondary syphilis, the more immunity is developed to late manifestations of the disease, especially in the central nervous system. In other words, marked secondary reactions of the skin are believed by many observers to result in an increased ability of ectodermal tissues to resist the infection. This observation does not hold true for all individuals with florid secondary skin reactions, but it may well have significance. The early stages of syphilis represent a very important period in the development of immune changes in the host.

Duration of secondary manifestations.—As a rule, the secondary lesions of syphilis are not destructive, and they heal without scar formation. Like the primary lesions, secondary manifestations are self-limited and heal in varying periods of time without treatment. Usually secondary manifestations disappear within a few weeks or months, but occasionally they persist for as long as a year or more. I once saw an untreated male patient who still had dark field positive secondary lesions 11 months after he had first noticed a skin eruption. The history seemed to be reliable in this case, but there was no way of confirming it, as no previous diagnostic studies had been made. The patient had had a succession of lesions, starting with a genital sore followed by a generalized eruption, periostitis, and a sore throat. The skin manifestations had healed when I saw him, except for condylomata between the toes, which swarmed with T. pallida. He still had a sore throat and mucous patches in the throat 11 months after the onset of his eruption. This case is not representative of relapsing early syphilis but of a continuation of the clinical stage of secondary manifestations, because the patient had not been free of symptoms at any time since the onset of his eruption.

As a matter of fact, I have never seen true clinical relapses of secondary

syphilis except in patients who had had insufficient treatment during the early stages of the disease. I do not believe that relapses occur in the untreated stage of secondary syphilis. During the untreated secondary stage lesions may appear progressively in different sites, but the progressive manifestations are not evidences of relapse but of a persistence of secondary syphilis.

The termination of secondary syphilis in an immunologic sense.—From a clinical point of view secondary syphilis terminates when all demonstrable secondary lesions have completely disappeared. In an immunologic sense, the secondary stage of syphilis terminates only when the body tissues have attained a permanent refractory state toward early infectious lesions.

Refractory state toward early syphilitic lesions.—*To understand the foregoing statement it is necessary to know that within 2 years after infection, untreated syphilis produces immunologic changes in the host which with rare exceptions are permanent and make it impossible for the tissues to react to subsequent infection with the development of early syphilitic lesions Thus after the immunologic changes have become established regardless of whether or not the syphilis is subsequently cured reinfection may occur but it occurs without the development of primary or secondary lesions On the other hand if the patient is treated before the refractory state is permanently established reinfection or relapse is usually followed by the development of new early lesions*

Time required for the development of refractory state.—The period required for the attainment of the refractory state in untreated individuals undoubtedly varies greatly and may be as long as 2 years in some cases. In most individuals permanent "immunity" to the redevelopment of early lesions probably occurs in much less than 2 years, but one cannot be certain in all cases that the refractory state is established by the time clinical signs of secondary syphilis can no longer be demonstrated.

My belief that the refractory state toward early lesions is permanently established within the first 2 years of untreated infection is founded on the following observations

During the past 10 years we have seen at Bellevue Hospital approximately 2,000 cases of infectious relapse or reinfection following some form of previous treatment for early syphilis. A review of the records reveals that all but a few of this group (not more than 20) had primary or secondary lesions at the time of their original treatment. In the few exceptions, secondary lesions had healed by the time the patients had their original treatment but the time of treatment was still within 2 years

following infection. The fact that these few patients had new dark field positive lesions at the time of their relapse or reinfection proves that the refractory state toward early lesions is not permanently established in some cases by the time the original secondary lesions heal but it is permanently established within 2 years.

Among many thousands of patients who had dark-field positive lesions when seen at Bellevue Hospital during the past 10 years, all but one had a first infection or had a relapse or reinfection following treatment received within the first 2 years after the original infection. The one exception was a colored male, 51 years of age, who was first treated in Atlanta, Ga., 15 years after he acquired a penile lesion. When syphilis was diagnosed, he already had cardiovascular involvement with aortic insufficiency. In Atlanta he received 80 injections of arsenical drugs and 125 injections of bismuth from 1935 to 1937. On his return to New York City he continued to receive some treatment at local clinics until 1943. Negative serologic tests for syphilis were reported in 1943 and 1944 following his probation from antisyphilitic treatment. In April, 1945 he was admitted to Bellevue Hospital with a dark field positive penile lesion, and his serologic tests for syphilis had again become positive. Obviously he had been reinfected or superinfected and had responded with the development of another chancre in spite of the fact that he had received no antisyphilitic treatment for the first 15 years of his infection. If the vast majority of infected individuals did not acquire a permanent refractory state toward early lesions after 2 years of an untreated infection, we would have seen many more instances such as the one described above.

Such observations lead to the conclusion that individuals who receive no antisyphilitic treatment for 2 years following infection, with extraordinarily rare exceptions, will never again react to the syphilitic virus with early dark-field positive lesions, even though reinfected or superinfected with heterologous treponemes. The establishment of the refractory state does not mean that patients who are cured after 2 years of infection are immune to syphilis; it only means that their tissues will no longer react with the development of early lesions.

It is important to understand the immunologic changes which occur during the early stages of syphilis because the establishment of these changes terminates what might be called the acute phase of the infection. Thereafter the responses of the body tissues to the syphilitic virus are quite different. During the first 4 to 10 weeks of the acute phase, tests for syphilis of the blood serum become positive. By the time secondary lesions appear the serologic tests have been positive in 100 per cent

of the patients observed at Bellevue Hospital during the past 12 years. This is one of the very few rules in syphilis that, in my experience, has had no exceptions, but, according to both Moore and Stokes, authentic cases of secondary syphilis with negative serologic tests have occurred

INFECTIOUS RELAPSES

To discuss infectious relapses of early syphilis, I will have to digress from the course of untreated syphilis, because early syphilis cannot be said to relapse except after treatment. As previously stated, the manifestations of secondary syphilis do not necessarily appear simultaneously The first lesions to appear may be healing when new lesions at a different site are forming but the latter are not evidences of relapse they are only a progression of the secondary manifestations. The reappearance of early dark field positive lesions weeks or months after all previous early lesions have healed is a genuine relapse or reinfection, but such lesions occur only in patients who have been treated for early syphilis.

Cause of infectious relapses.—Antisyphilitic treatment which fails to cure early syphilis destroys large numbers of treponemes, but a few survive. Presumably the surviving organisms have been injured by the therapy and are unable to multiply for varying periods of time after treatment has been completed. The fact that most of the treponemes have been destroyed reduces the stimulus to the formation of reagin to a minimum, with the result that quantitative serologic tests for syphilis following therapy drop rapidly In some cases the tests may even become negative before the few surviving treponemes revive, multiply at a normal rate, and are redisseminated by the blood and lymphatics, with the result that reagin is again produced in large amounts, and the body tissues react with early infectious lesions. We have no knowledge of the actual status of the treponemes during the period between the completion of treatment and a demonstrable relapse. By the time early lesions of syphilis appear the body has already developed some immunologic changes, but they are not permanently established The killing of large numbers of treponemes definitely retards the production of a permanent refractory state toward early lesions, and treatment which cures early syphilis prevents the development of this immunologic change. Such immunologic changes as may have occurred prior to treatment of early syphilis rapidly disappear uncured patients may relapse with infectious lesions, and cured patients will usually react to reinfections with the redevelopment of early lesions. We do not know how long T pallida can remain in the body without divid-

ing but it is most unlikely that infectious relapses have ever occurred 2 years or more after the completion of treatment of early syphilis we know from clinical experience that most relapses occur between the third and ninth months after intensive therapy At Bellevue Hospital we have observed new infectious lesions in patients within 5 or 6 weeks after the completion of therapy Dr Simeon Landy who has examined most of these patients and taken careful histories from them, believes that all of them were reinfected. In his opinion and mine, reinfections may occur *within a few days after penicillin therapy of early syphilis with the subsequent development of lesions*, but, in our experience, relapses rarely occur before 8 weeks after treatment.

Infectious relapses during or after the older types of prolonged therapy—Prior to the advent of rapid treatment of early syphilis, infectious relapses were frequently seen during the course of irregular treatment with heavy metal and arsenical drugs. Patients who failed to receive treatment for several weeks or months and patients who received very small doses of arsenical drugs often suffered repeated infectious relapses. In some cases relapses recurred over as long a period as 4 or 5 years. Because infectious relapses were not uncommonly observed up to 5 years after infection during irregular treatment, most syphilologists in the past taught that secondary syphilis might relapse over a period of 4 to 5 years. Actually the delay in the development of this immunologic change beyond 2 years was due to the interference of inadequate and irregular treatment. With the older methods of prolonged therapy patients frequently lapsed from treatment, only to return when relapsing early lesions appeared. After treatment had caused the lesions to disappear the patients again lapsed from regular therapy with further infectious relapses. This train of events in some cases continued for at least 4 to 5 years, provided patients had not lapsed from all therapy for at least 2 years. Another cause of infectious relapse with the older forms of treatment was the fear of reactions to arsenical drugs, with the result that some patients were treated with very small doses. In such cases relapses occurred during the course of *regular treatment. Therefore, irregular or* inadequate treatment of early syphilis prolongs the period of relapsing infectious lesions long after a permanent refractory state would have been established without treatment.

Infectious relapses and rapid therapy—Similarly after rapid therapy of early syphilis, patients who failed to be cured relapsed in varying periods following treatment. Most relapses after rapid treatment of early

syphilis have occurred between the third and ninth months after the completion of treatment. Some infectious relapses have undoubtedly occurred during the second year after treatment, but, as previously noted, I doubt that such relapses can occur 2 years or more after the completion of therapy At present one cannot make a definite statement to this effect because of the impossibility of differentiating in all cases between relapses of early syphilis and reinfections. In my experience, the histories and clinical manifestations of patients who have developed new infectious lesions 2 years or more after rapid treatment of early syphilis favor reinfection rather than relapse.

One patient, still under observation at Bellevue Hospital, has been given rapid treatment for dark-field positive early syphilis five times during the past 5 years. The dark field positive lesions may have been evidences of relapse or reinfection, but in either case repeated courses of treatment prevented the permanent acquisition of "immunity" to early skin and mucous-membrane lesions, with the result that these tissues continued to respond to T pallida with early lesions.

SEROLOGIC RELAPSES

Just as some individuals acquire syphilis without demonstrable early lesions, some individuals may relapse after unsuccessful therapy of early syphilis without apparent clinical manifestations. In such cases the relapse can be determined by quantitative serologic tests for syphilis. If the titrated serologic tests for syphilis have become negative or show a definite trend toward negativity and then reverse to positive or to much higher titers *and maintain these higher levels, the patient has had a serologic* relapse and must be retreated. The absence of demonstrable lesions in such cases does not necessarily mean that the patients are not infectious by sexual contact. Many of them undoubtedly are infectious, even though the examining physician fails to observe lesions. I am convinced that in some cases women may harbor treponemes in the cervix or elsewhere in the genital tract without having detectable lesions. Similarly men may have treponemes in the semen during a relapse following treatment of early syphilis, even though no lesions are evident.

In some cases a rise in the titer of the quantitative serologic tests precedes the appearance of a clinical relapse after treatment of early syphilis. If such a patient is re treated inadequately for a serologic relapse, a second relapse with infectious lesions may occur I have observed this phenomenon in a number of patients who were first re treated for serologic relapses and later for relapses with dark field positive lesions.

DANGER OF EARLY INADEQUATE TREATMENT

The point to fix firmly in mind with respect to the somewhat confusing phenomena of relapsing early syphilis is that inadequate treatment during the early stages of infection interferes with the production of permanent "immunity" to the development of early lesions and probably with that of other immune reactions in the host. As a result, patients may have infectious relapses and later may develop serious late lesions of syphilis, if the relapse was undetected. This fact explains the old dictum that inadequate therapy of early syphilis may do more harm than good, and also explains why it is so essential to keep patients under observation for long periods after treatment is completed.

FIG. 1 SUMMARY OF IMMUNOLOGIC CHANGES DURING EARLY SYPHILIS

1. With extremely rare exceptions, permanent refractory state toward early lesions is established within 2 years of an untreated syphilitic infection.
2. The so-called immunity to the development of early lesions in no way implies immunity to T pallidum infection; it means only that the body tissues will no longer react to the syphilitic virus with early infectious lesions characteristic of the acute phase of syphilis.
3. Patients who are not cured by rapid treatment during the early stages of syphilis may elapse with infectious lesions at any time up to at least 2 years after treatment, but the majority will relapse during the first yea If re-treatment fails to cure the patient, subsequent infectious relapses may occur after the re-treatment.
4. Patients who are cured by rapid treatment during the early stages of syphilis can be einfected t any tim after treatment and may respond with the development of new chancres and/or secondary lesions.
5. Relapses after rapid treatment of early syphilis can be detected in some cases only by quantitative serologic tests for syphilis.

LATENT SYPHILIS

Now that the problem of relapsing early syphilis has been presented, we again follow the course of untreated syphilis and consider the so-called latent period. Latent syphilis is the asymptomatic stage of the infection, diagnosed solely by the presence of positive tests for syphilis in the blood serum and by history However before this diagnosis is acceptable, in addition to the physical examination, a spinal-fluid examination and X-ray

or fluoroscopic examination of the heart and aorta must have been found to be negative for syphilis. If the spinal-fluid findings are abnormal, the diagnosis is not latent syphilis but asymptomatic neurosyphilis. The differentiation of latent syphilis from asymptomatic neurosyphilis is important because the latter has a more serious prognosis.

By definition, then, latency is a clinical term used to classify that large group of patients who are said to have syphilis because of positive serologic tests, or because of a past history of infection Since some individuals have positive serologic tests for syphilis as a result of conditions unrelated to syphilis (biologic false positive tests) and other patients who have had adequate therapy continue to have positive serologic tests for syphilis long after the infection has been arrested it is apparent that the diagnosis of latent syphilis can only be made after careful histories have been taken and thorough physical examinations have been made. At present, however we are concerned only with the possible course of known untreated syphilis, and particular problems of diagnosis must await more detailed consideration.

When does latency begin clinically?—Clinically the latent stage of syphilis can be said to begin as soon as the serologic tests for syphilis become positive in individuals who have no manifest lesions. In those who have early lesions, the period of latency follows the disappearance of the lesions, with the further proviso that the spinal fluid and cardiovascular system are found normal on examination.

When does latency begin immunologically?—Actually from an immunologic point of view latent syphilis begins only when patients have developed a permanent "immunity" to the formation of early lesions. As previously noted, it is impossible to know in all cases when this type of "immunity" becomes firmly established. If one accepts 2 rather than 4 or 5 years as the outside limit for the development of a refractory state toward early lesions in untreated individuals, latency in an immunologic sense, may not begin in some cases until 2 years after infection The majority of infected individuals who are untreated probably enter the immunologic status of latency very soon after all secondary lesions have healed, which usually occurs within the first year after infection.

Latency and the activity of infection.—The term latency as used clinically does not refer to the activity of the syphilitic infection since the latter is beyond clinical determination. In fact, during the latent stage there may or may not be active syphilitic inflammatory foci in the body Consequently it is not correct to regard latent syphilis as a relatively harmless condition

Moore has noted that many patients treated for latent syphilis volunteer the information that treatment made them feel better and my own observations have borne this out. In some cases the improved sense of well-being was probably psychologic, but in others it was undoubtedly a result of the specific effects of therapy

Thus, it is obvious that we cannot predict the outcome of the latent infection in an individual patient. We know that individuals vary enormously in their ability to resist the infection. Some will develop mortal organic disease, others will escape with insignificant damage. Even in a given individual the reaction to T pallida undoubtedly varies from time to time during latency with the result that there may be periods when inflammatory foci are quiescent or relatively static and other times when an active and progressive inflammation is present. As will be shown later in the case of neurosyphilis we have fairly accurate guides in the spinal fluid to the activity of a syphilitic process within the central nervous system. Unfortunately in latent syphilis no such aids are available.

Outcome of latent syphilis.—Latent syphilis may have one of three different outcomes (1) It may persist as such throughout the life of the infected individual (2) it may result in the development of signs and symptoms of late syphilis (3) it may terminate with the spontaneous cure of the infection.

It is impossible to give accurate statistics for these three possible eventualities of untreated latent syphilis. Moore has estimated that untreated individuals with latent syphilis have about one chance in four of developing serious organic disease. Jordon and Dolce reported on 169 patients with latent syphilis observed for 10 years or more. They found that between 20 and 25 per cent of those "poorly treated" developed some late complication. These estimates that about 25 per cent of untreated or poorly treated individuals with latent syphilis progress to some symptomatic phase accord well with the estimate that from 60 to 70 per cent of all untreated syphilitics will develop no diagnosable late manifestations of the disease apart from positive serologic tests.

The estimate that from 60 to 70 per cent of untreated syphilitics will develop no demonstrable late lesions is made from a variety of data none of which afford scientific proof on a sound statistical basis. By reviewing several thousand records of patients with latent syphilis, if one chooses only those individuals who probably acquired syphilis as relatively young people but failed to be treated until late in life, one can readily hazard the guess that from 60 to 70 per cent of untreated syphilitics remain asymptomatic.

The nearest approach to a scientific experiment based on the observation of a large group of individuals diagnosed as being syphilitic but deliberately left untreated is that reported by Bruusgaard. In the latter part of the nineteenth century and early part of the twentieth century Boeck of Oslo deliberately refused to treat a large number of patients whom he diagnosed as having syphilis because he believed the treatment then used was worse than the disease. In 1929 Bruusgaard reported follow-up observations on all of Boeck's untreated patients who could be located. The observations cannot be said to meet the requirements of statistical validity because the untreated individuals who were located probably do not represent a true sample of the entire group. Nevertheless, the figures given by Bruusgaard confirm the impression given above—that from 60 to 70 per cent of untreated syphilitics never develop late manifestations of the disease.

The same figures are further supported by Rosahn's autopsy findings on 380 syphilitics, 198 of whom never received treatment. Anatomic lesions of syphilis were found in 38.9 per cent of the untreated individuals and no lesions were found in 61.1 per cent.

Spontaneous cure of syphilis.—How many individuals achieve spontaneous cure of syphilis without treatment cannot be determined from available data. In the series reported by Bruusgaard as high as 28 per cent of the observed patients apparently had spontaneous cures, as indicated by negative serologic tests for syphilis and normal physical examinations. However the original diagnoses may have been in doubt in some of these cases.

Difficulties of proving spontaneous cure of syphilis.—The fact that no pathologic evidences of syphilis were found in 61 per cent of untreated syphilitics by Rosahn is, of course, not offered by him as proof that the infection was cured in these cases. Treponemes may well persist during the period of latency in many individuals as relatively innocuous saprophytes. Chesney proposed this possibility in his monograph on "Immunity in Syphilis," and it is the most plausible explanation for some of the phenomena observed in the course of the disease. For example, I once saw a patient who developed tertiary syphilides of the skin late in life. He died soon after the skin lesions had healed with antisyphilitic treatment. The pathologist reported no evidences of syphilis at autopsy except for the scars of the healed skin lesions. Yet this man must have harbored treponemes for many years, and one can scarcely believe that the therapy given for his late skin manifestations could have obscured all other pathologic evidences of the infection. The treponemes must have been present for years,

as relatively harmless parasites prior to the development of late tertiary allergic lesions in the skin.

The fact that no syphilitic lesions were found at autopsy in this known case of late cutaneous syphilis does not prove that all untreated infected individuals harbor the syphilitic virus for life. Syphilis is an extraordinarily complex and varied disease, and one is never justified in making generalizations about it without abundant evidence. It may even be true that some syphilitic infections are completely eradicated without therapy in the continued presence of positive reactions for syphilis of the blood serum. The persistence of such positive reactions, as we will have occasion to see later cannot be accepted as proof of a continued infection.

Infectiousness of latent syphilis.—As nearly as can be determined, latent syphilis is not infectious in most cases, even by sexual contact, but I am convinced that this is by no means always true. A number of patients at Bellevue Hospital have given as sources of infection individuals with latent syphilis. To be sure, one cannot trust the histories given by patients in all cases, but there could be little doubt of the accuracy of the histories in some of the cases. In 1937 four boys in their early teens were admitted to Bellevue Hospital with secondary syphilis. They all gave the same woman as the source of their infection and claimed that they had had sexual exposures to no one else. The woman in question was found and examined. She presented no lesions of syphilis and gave a history of having discovered that she had positive serologic tests for syphilis 5 years previously She had received about 10 injections of bismuth at that time. Her serologic reactions were still strongly positive when examined at Bellevue Hospital, and the spinal fluid was normal. She had no lesions on the external genitalia or cervix. *Efforts were made to find T pallida in the* secretions from the intact cervical canal without success. She verified the stories of the four boys and volunteered the belief that their first sexual exposures were with her The question was how she infected the boys when she had latent syphilis of more than 5 years duration. As she was admittedly promiscuous, perhaps she had been infected with T pallida numerous times after her original infection, and treponemes may have lived for varying lengths of time in the cervical canal or genital tract without causing perceptible lesions Instances such as this are difficult to explain otherwise, but one cannot deny the possibility that latent syphilis is infectious in some cases, even though we cannot explain how it is infectious. In the case of males it has long been suggested that the semen of late syphilitics might contain T pallida. Kemp failed to find treponemes in 100 specimens of semen of males with late syphilis, but this

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tral nervous system can be detected by spinal fluid study in the absence of all signs and symptoms of central nervous-system involvement. Such precise tests are not available for subclinical syphilitic lesions of other tissues, with the result that an inflammatory focus may elude detection until sufficient damage has occurred to produce diagnosable signs on physical or X-ray examinations. Clearly spinal-fluid tests afford a unique opportunity to study the course of syphilis in at least one important system of the body

Significance of spinal-fluid examinations.—Experience has proved that the spinal fluid reflects the activity of syphilitic inflammatory processes in the central nervous system with amazing accuracy Dr Bernhard Dattner who assisted Wagner Jauregg in Vienna with the earliest trials of malaria treatment of general paresis, first pointed out the full implications of this statement. Since 1938 Dattner has continued his study of neurosyphilis at Bellevue Hospital, and I have worked in close association with him. As a result, I have been convinced of the accuracy of his conclusion that the activity of a syphilitic inflammatory process in the central nervous system is clearly and consistently demonstrated by spinal-fluid tests. Exceptions to this rule may be found, but they are rare. As will be shown in subsequent chapters, following antisyphilitic treatment, serologic tests for syphilis, unless done quantitatively give no information about the activity of a syphilitic process spinal-fluid examinations, on the other hand, tell us a great deal about the activity of a syphilitic process in the central nervous system.

Onset of syphilitic inflammations of central nervous system.—It is generally acknowledged that in untreated syphilis, if the spinal fluid is normal 4 or 5 years after infection, it will not become abnormal because of syphilis. My own impression is that in most untreated cases the spinal fluid will reveal the presence of neurosyphilis by the end of 2 years or not at all. As with relapsing secondary syphilis, the period of 2 years may be extended to 4 or 5 in patients who receive irregular and inadequate therapy during the first 2 years of infection. In other words, in many untreated individuals the central nervous system establishes a permanent immunity to syphilis during the first 2 years of infection. Inadequate therapy can interfere with the production of this immunity and prolong the period during which it is established. But in all cases, with possible rare exceptions, a normal spinal fluid 5 years after infection means permanent immunity to neurosyphilis. Thus, patients with normal spinal-fluid tests for syphilis 4 or 5 years after infection do not require repeated spinal-fluid examinations to rule out neurosyphilis, but those individuals who have

abnormal spinal-fluid tests for syphilis 4 or 5 years after infection will in most cases continue to have syphilis of the central nervous system unless they receive proper treatment.

Duration of asymptomatic period.—In spite of the fact that neurosyphilis begins its course during the early years of infection, individuals with positive spinal fluid findings for syphilis may remain asymptomatic for many years. The vast majority of infected individuals who develop neurosyphilis pass through a period when the only evidences of central-nervous-system involvement are the abnormal spinal fluid findings. As with all syphilis, the duration of the asymptomatic period of neurosyphilis varies greatly in different individuals. In many cases more than 20 years may elapse before the patient seeks medical assistance for the symptoms of central-nervous-system syphilis, and even then the diagnosis may be obscure and may be missed for the lack of spinal fluid examinations. In such cases, had the spinal fluid been examined at any time after the first few years of infection, the central-nervous-system involvement could have been detected in its asymptomatic phase. Neurosyphilis can be diagnosed earlier and more accurately than can syphilis of the cardiovascular system and late syphilis of the internal viscera.

LATE SYMPTOMATIC SYPHILIS

The late lesions of syphilis differ from those of the primary and secondary stages in two important respects (1) late lesions are destructive and (2) they are chronic. They represent a very different immunologic response to the syphilitic virus than do early lesions. In general, the late manifestations of syphilis are caused by two different types of inflammatory response (1) foci of chronic, diffuse, granulomatous inflammation (2) explosive allergic reactions resulting in granulomas known as gummas.

Histologically both types of inflammation present a similar picture, with the difference that many gummas are discrete, tumorlike masses which may be microscopic or macroscopic in size. Clinically the difference between the two responses is sufficiently marked to raise numerous questions about their onset and origin. But before discussing the clinical aspects of late symptomatic syphilis, it is well to know something about the pathology of late lesions.

PATHOLOGY

The histologic picture of late syphilitic lesions is essentially that of any

chronic inflammation, viz., infiltration of tissues with mononuclear cells, predominately lymphoid in type but with most of the mononuclear cells being represented in varying degrees. The presence of plasma cells is especially characteristic of syphilis, as are increased vascularity and perivascular infiltration or cuffing of small blood vessels with mononuclear cells. Giant cells are commonly found in gummas, but they are not always found in pathologic sections of gummatous tissues. As a matter of fact, other agents than T pallidum may cause chronic inflammatory changes similar to those seen in syphilis. Foreign bodies can produce inflammatory reactions similar to those of gummas. Certain virus infections and chronic poisoning with toxic agents such as arsenic can produce cellular infiltrations in the brain and other tissues similar to those of syphilis. Consequently it is unfair to expect a pathologist in all cases to make a definite diagnosis of syphilis from the histologic changes observed in tissue sections. In my experience, it is not always possible for pathologists to do more than report chronic inflammatory tissue when examining biopsies of lesions which were unquestionably syphilitic judging from the response to antisyphilitic therapy In such cases a therapeutic test with antisyphilitic treatment is more helpful than a pathologic report.

In most cases at post-mortem examination, the pathologic changes due to syphilis can be fairly accurately identified, because syphilis is by far the commonest cause of chronic specific inflammation apart from tuberculosis, the pathology of which is usually more specific than that of syphilis. Also acid-fast bacilli are, as a rule, more easily demonstrated in tuberculous tissues than are treponemes in late syphilitic lesions. In certain tissues, such as the aorta and bones, syphilis causes changes so characteristic and unique that the diagnosis can be made with reasonable assurance by pathologists, but not infrequently in other tissues the etiology of the changes observed may be controversial. Most pathologists, however are convinced that a preponderance of small round cells and plasma cells together with an overproduction of fibrous tissue and increased vascularity make the diagnosis of syphilis reasonably certain

Warthin, in numerous reports, maintained that syphilis produces widespread injury and cellular infiltration in many organs, and that this is generally overlooked. He found areas of fibrosis and old scars infiltrated with plasma and lymphoid cells at many different sites. With astonishing frequency he was able to demonstrate treponemes in stained sections of tissues showing chronic inflammation. Other pathologists have been more skeptical about diagnosing syphilis in pathologic specimens, and they have been unable to find treponemes with the frequency that Warthin

found them. Thus, in spite of the enormous amount of syphilitic material which has been available to pathologists over a period of many years, syphilis, on occasion, still continues to evade absolute identification even with biopsies and post mortem examinations.

For the inquiring mind, no common disease is so exasperating and at the same time so fascinating as syphilis because of its ability to simulate so many other conditions even at post-mortem examination. No other common disease is so elusive or so replete with controversial problems. Because of its exquisite chronicity during the long course of infection numerous other pathologic conditions may be superimposed on syphilis. It follows that in doubtful cases both syphilologists and pathologists should have at their disposal the most exacting case histories before concluding that syphilis is the sole cause of the pathologic processes noted.

CLINICAL ASPECTS OF LATE SYMPTOMATIC SYPHILIS

As a general rule, overt manifestations of late syphilis do not appear until some 10 years after infection Many exceptions to this rule occur but in the majority of patients late syphilitic lesions are diagnosed between the tenth and thirtieth years after infection.

The search for explanations of the long delay in the appearance of late manifestations leads us into the fascinating but still obscure field of immunologic reactions designated as allergy It should be clearly understood, however that labeling phenomena does not explain them. At present no field of medical research offers more complex and diversified problems than that of allergy The mechanism underlying the alterations of tissue sensitivity to a great variety of antigens is still not clearly known, *and the principles underlying a host of varied reactions designated as* allergic do not yet explain all of the phenomena observed.

In this section on the clinical aspects of late symptomatic syphilis my purpose is less to discuss details of diagnosis than to present the problems created by the great variety of the phenomena. To understand the problems, even if we cannot explain all of the observed phenomena, we must know in general the types of late syphilitic reactions which may occur and what tissues are most likely to be involved by late syphilis.

As previously noted the late lesions of syphilis can be divided into two groups (1) chronic diffuse inflammations and (2) gummas. The typical examples of chronic diffuse inflammation occur in the central nervous system and aorta We know from spinal-fluid examinations that the inflammatory changes in the central nervous system begin during the early

years of infection, and, from the evidence of thousands of autopsies, the same is probably true of syphilis of the aorta, but symptoms may not become apparent in either case for many years after infection. A gumma, on the other hand, has a sudden onset, usually late in the course of the disease, and it may or may not produce symptoms at its onset. The typical gumma is a discrete granuloma which varies in size from a microscopic unit to a large tumor

In addition to the typical discrete gumma, late gummatous infiltrations may develop which are similar to the chronic diffuse inflammation observed in the central nervous system and aorta they are usually included with gummas because, in most cases, they apparently have a sudden onset like that of the discrete gumma. Whether or not late syphilis causes a continuous low-grade chronic inflammation from the early years of infection in tissues other than the vascular and central nervous systems is difficult to determine. To investigate this problem further let us examine the general characteristics of gummas and gummatous reactions.

GUMMAS

Even when the histologic picture is not absolutely specific, a typical gumma can usually be recognized by pathologists because of its discrete character During life, when a gumma can be seen or palpated, the nature of the lesion is usually suspected if the patient is known to have syphilis. A typical gumma of the skin starts as a swelling which rapidly breaks down to form an ulcer The same is true of a gumma of the tissues of the nose and throat, and of the internal organs which have a lumen, such as the esophagus, stomach, and bladder In organs such as the liver and testes, a gumma forms a small or large tumor As a rule, the clinical picture of a gumma is not pathognomonic, and the diagnosis must frequently be established by means of serologic tests and a therapeutic test. If the lesion responds to antisyphilitic treatment, the syphilitic etiology is usually considered established.

Diffuse gummatous infiltration has a similar histologic picture to that of a discrete gumma, but, clinically it presents a different appearance. In the skin the more diffuse infiltrations cause lesions known as noduloulcerative syphilides, which consist of nodules which may or may not ulcerate, and which usually occur in groups having an arcuate or polycyclic configuration. All tertiary syphilides of the skin are destructive and heal with scar formation. They are chronic and may heal spontaneously in the course of months, only to have new lesions break out in the edge of the healed areas.

The two types of cutaneous gummatous reactions apparently have their analogue in most other tissues of the body Discrete gummas of the mucous membranes or bones of the nose, mouth, and throat produce ulcers. Perforating ulcers of the nasal septum and hard and soft palate are not infrequent in late syphilis. The more diffuse type of infiltration causes swelling of the tissues, with or without superficial ulceration. In the bones discrete gummas produce localized areas of bone destruction (syphilitic osteomyelitis) while the more diffuse type of infiltration causes proliferative changes with increased density of the involved bone. Both destructive and productive changes may occur in the same bone. In the stomach a discrete gumma forms an ulcer simulating the ordinary peptic ulcer while the diffuse type of infiltration may involve large areas of the stomach wall, especially in the midgastric and prepyloric areas. Similar tissue reactions of late syphilis could be described in most of the organs except the intestines and ovaries which apparently escape demonstrable syphilitic lesions entirely It is not my intention in this chapter to describe the late manifestations of syphilis in detail. At present we are interested only in the general features of the lesions, and especially in when and why they begin.

When do gummas occur after infection?—*I have not seen gummas* during the first 2 years of a syphilitic infection. Occasionally during the early years, especially of irregularly or inadequately treated syphilis, lesions of the skin are seen which are borderline in appearance between secondary and tertiary lesions (precocious tertiarism) Such lesions are nodular and may occur in groups, but they are not so destructive as true tertiary syphilides. In most cases gummas occur after 5 years of infection, and, in my experience, they are most frequently seen from the tenth to the thirtieth years after infection.

Gummas and allergy—The relatively sudden explosive onset of gummas years after infection together with the small number of treponemes found in them are reasonable evidence that gummas are due to *altered reactions of tissues sensitized to the syphilitic virus. If further confirmation* is desired, the reader is referred to the experiments of Finger and Landsteiner who injected T pallida into the skin of human beings who already had tertiary skin lesions, with the result that 13 of 15 individuals inoculated responded with the development of gummatous skin lesions.

Treponemata pallida have never been found by dark field examination of the serum taken from gummas of the skin or mucous membranes, and they are found with great difficulty in stained sections of gummatous

tissues. It is assumed, therefore, that the affected tissues reacted suddenly and violently to the presence of a very few treponemes.

Whether or not the treponemes causing gummas have been present in the affected tissues throughout the course of the infection is unknown. To me it seems unlikely that treponemes remain in the skin, for example, as innocuous parasites for years, only to have the skin become sensitized and react to their presence with a gumma. I think a more plausible explanation is that gummas are the result of impact between sensitized tissues and treponemes which have recently reached these tissues by way of the blood stream or lymphatics. Treponemata pallida are undoubtedly transferred by the blood and lymphatics from one site of infection to another site in the body during the long course of syphilis.

Does the diffuse type of gummatous infiltration in tissues other than the aorta and central nervous system have a sudden onset as a result of sensitization of affected tissues?—I do not believe that this question has been satisfactorily answered. In my experience, the clinical manifestations of late diffuse lesions of syphilis in tissues other than the aorta and central nervous system have had a relatively sudden onset late in the course of the disease, similar to gummas. Except in the skin and accessible mucous membranes, it is usually impossible to determine from the clinical manifestations alone when the lesions of late syphilis actually begin. It is, of course, possible that a very low-grade, diffuse, inflammatory reaction may exist for years before it can be demonstrated during life. This may be true of the diffuse syphilitic lesions of bones and viscera, but there is no question that sudden exacerbations occur which produce demonstrable lesions and symptoms. From analogy with neurosyphilis, we might well conclude that a demonstrable late syphilitic osteitis must have actually started during the early years of infection. On the other hand, from analogy with late cutaneous syphilides, even the productive type of osteitis may have a sudden onset as a result of altered sensitivity of the bone. I could cite numerous case histories which show a relatively sudden onset of demonstrable late diffuse syphilitic inflammation in body structures which had previously appeared to be normal. To illustrate this point I give the relevant facts of the following two cases.

Case 1. In 1938 an Italian woman, 63 years of age, was admitted to Bellevue Hospital because of sudden onset of pain in both thighs. X-ray films of the bones revealed marked osteoplastic osteitis and periostitis of both femurs. She was known to have had syphilis since the age of 22 and she had received scanty irregular antisyphilitic treatment during the early years of the infection. At the age of 58, 5 years before the sudden onset of pain in her

thighs, because of pelvic pain she had a roentgenogram of her pelvis, which included the upper thirds of both femurs. No signs of osteitis were noted at that time, and the roentgenogram revealed no abnormalities of the upper portion of the femurs. Five years later X ray films showed a marked productive osteitis and periostitis of the entire shafts of both femurs. Marked symptomatic improvement occurred following the onset of antisyphilitic treatment.

Case 2. In 1937 a white male was admitted to Bellevue Hospital with the chief complaint of inability to retain solid food for the past 1½ years. He gave a history of a penile lesion during World War I but he had never received antisyphilitic treatment. Two years prior to his admission to Bellevue Hospital because of gastric complaints, he had a gastrointestinal X ray series while attending the Out-patient Department of Bellevue Hospital. The roentgenograms of the stomach and intestines at that time revealed no abnormalities. On his admission to the hospital 2 years later the gastrointestinal X rays showed marked narrowing of the prepyloric portion of the stomach and 8-hour retention of the barium meal. The presumptive diagnosis of the roentgenologists was scirrhous carcinoma. In view of the positive serologic reactions for syphilis and the previous history he was given antisyphilitic treatment, with dramatic improvement of his symptoms. He was observed by gastroenterologists as well as syphilologists during his stay in the hospital, and the final opinion of all was that he had diffuse syphilitic infiltration of the distal third of the stomach Six years later his gastrointestinal series still showed narrowing of the prepyloric portion of the stomach as a result of scar tissue, but he had no retention of the barium meal, and he was entirely free of symptoms.

The above cases demonstrate that signs and symptoms of the diffuse type of inflammation may have a sudden onset very late in the course of infection. Whether or not the femurs in Case 1 and stomach in Case 2 *had syphilitic foci for 30 and 20 years, respectively without signs or* symptoms, cannot be determined. It is probable, however that the reactions were similar in onset to those of the more typical gumma.

CHRONIC DIFFUSE INFLAMMATION OF THE CARDIOVASCULAR AND CENTRAL NERVOUS SYSTEMS

Syphilitic inflammations of the aorta and central nervous system are not only the most frequent manifestations of late syphilis, but they are also the most serious. In both cases the inflammation begins during the early years of infection soon after the secondary stage is completed. Yet, in both cases, clinical signs and symptoms are not usually apparent for at least 10 years after infection I shall not discuss the details of syphilis of the cardiovascular and central nervous systems in this chapter but shall touch on certain special features presented by late syphilis in these systems.

By cardiovascular syphilis we usually mean syphilis of the aorta and aortic valves. Single or multiple gummas may rarely develop in the myocardium, but most syphilitic heart disease has its origin in the aorta. A vasculitis or endarteritis is found in all late syphilitic lesions, including those in the wall of the aorta. But, for reasons unknown, syphilis of the larger vessels, apart from the aorta is relatively rare. Hemiplegia has been caused by vascular thromboses or hemorrhages due to syphilitic vascular changes, and, very rarely gangrene has been reported as a result of syphilis of one of the medium-sized peripheral vessels. Aneurysms caused by syphilis of vessels other than the aorta are occasionally found, but in the great majority of cases late syphilis of the vascular system affects only the aorta and the very small vessels which are involved in all syphilitic inflammations.

The wall of the aorta is probably invaded by treponemes during the early weeks of infection, but, so far as we know the chronic inflammatory reaction does not begin until after the secondary stage. Maynard has reported a death due to syphilitic aortitis and aortic insufficiency within 2 years after infection, but such a case is so rare that it must be classified as a freak. In general syphilitic aortitis can rarely be diagnosed during the first 10 years of infection, but the available pathologic evidence indicates that it begins during the first few years. I have seen typical microscopic syphilitic infiltration of the wall of the aorta of a patient who died from other causes within 3 years after a syphilitic infection. Reports from the large pathology clinics in Germany and Vienna also suggest that syphilitic aortitis probably starts soon after the secondary stage of the disease. It appears, then that the diffuse late syphilitic inflammation of the aorta has an early onset and runs an exquisitely slow and chronic course.

In the case of the central nervous system we have unquestioned evidence from the spinal-fluid examinations that late syphilitic inflammations (which vary markedly in their manifestations) begin during the early years of infection. If spinal-fluid findings are normal 4 or 5 years after a syphilitic infection, we can be reasonably certain that the central nervous system has permanent immunity to the disease. Yet clinical signs and symptoms of neurosyphilis are infrequently observed during the first 10 years of infection.

In spite of the long delay of symptoms, the chronic diffuse inflammation, which begins early in the course of late syphilis, apparently represents a different type of tissue sensitivity to treponemes than a gumma, which has an explosive onset. Unlike the diffuse inflammation, a gumma may develop in the central nervous system many years after infection.

The mechanism underlying the different reactions is unknown To call them different manifestations of allergy describes them rather than explains them.

Obviously a gumma is a late reaction caused by a relatively recent alteration of tissue sensitivity or to a recent contact of sensitized tissue with the T pallidum. The diffuse inflammation which starts early in the disease is a manifestation of the reaction of tissues which had inadequate resistance to the T pallidum from the beginning Such statements, however do not provide insight into the mechanism underlying the reactions. Almost every phenomenon caused by syphilis has been attributed to allergy because the most striking feature of syphilis is the changing reaction of tissues, but this statement leaves the most important questions unanswered. It does not tell us how or why the tissues alter in sensitivity nor does it explain the variety of pathologic manifestations which may develop in some tissues. As will be shown in later chapters, such phenomena as tabes dorsalis, optic atrophy and interstitial keratitis present unique pathologic processes in syphilis which as yet have not been satisfactorily explained. Factors other than allergy undoubtedly play a part in the various manifestations of late syphilis. Nevertheless, in spite of its inadequacy the concept of allergy cannot be dismissed in the attempt to understand syphilis of the cardiovascular and central nervous systems.

Chronic diffuse inflammation and allergy—Although syphilis of the aorta and central nervous system begins in the early years of infection, the signs and symptoms caused by the involvement of these tissues cannot be explained fully by regarding the inflammation as an exquisitely slow and gradual process which finally produces sufficient damage to cause clinical signs and symptoms. Rather we must think of the syphilitic process as a series of exacerbations and remissions which may in some cases, be the result of a varying sensitivity of the involved tissues. I have seen an aorta dilate markedly within 1 year late in the course of infection, and exacerbations and remissions of the symptoms of neurosyphilis are not uncommon.

According to Urbach and Beerman, the entire course of syphilis may be explained on the basis of allergy and Urbach defines allergy as "the inclusive immunologic concept which must therefore embrace all manner of states, ranging from the increased resistance to or tolerance of the action of pathogenetic agents, commonly called immunity or anergy to the hypersensitiveness due to sensitization of the organism (hyperergy)" *

U[illegible]ach E and Beerman H "The Present Status of Immunity and Allergy in Syphilis, *Am J Syph., G[illegible] & Ven. Dis* 31 193 1947

As previously indicated, this definition of allergy can be used to describe the course of syphilis, but it does not explain it.

We know that the early lesions of syphilis represent a different reaction than do the late lesions, and the course of late syphilis is marked by varying degrees of reaction. At least two factors must be considered in the attempt to understand the varying reactions in late syphilis (1) the sensitivity of the tissues to the treponemes, and (2) the virulence and number of treponemes present. Unquestionably body tissues vary from time to time in sensitivity to treponemes, but it is also true that the treponemes may vary in virulence, and they certainly vary in number from time to time. For example, in some cases of general paresis the brain may be swarming with treponemes, while in other cases the T pallidum is found with difficulty The mechanism underlying the tissue reactions and the rate of multiplication or death of treponemes is unknown.

Whatever the cause of the exacerbations and remissions of symptoms in chronic inflammations of the central nervous system may be, general paresis affords an excellent illustration of them. The onset of symptoms of general paresis may be insidious and gradual, or on occasions, dramatically sudden. When marked mental deterioration apparently occurs overnight, it is difficult to believe that the symptoms were caused by a slowly progressive inflammation which finally injured the brain sufficiently to produce insanity It is still more difficult to believe that the symptoms were due to the gradual injury of nerve tissue when the patient improves after antisyphilitic treatment or has a remission without treatment. The altered functioning of the nerve cells in such cases may be the result of a variety of factors, but one of the factors may be a changing sensitivity of the brain parenchyma to treponemes.

The concepts of anergia and hyperergia are useful in describing the course of syphilis, because we know that the human body and T pallida can live together in relative peace, provided nothing disturbs the harmonious relationship. Probably many factors, such as trauma and intercurrent diseases, can alter the defensive mechanism of the body but it is apparent that the body cells can be anergic or insensitive to the syphilitic virus, only to become hypersensitive at some times. Allergy must, of course, be interpreted relatively In most allergic diseases the sensitivity of cells to a specific antigen varies in degree from time to time. An explosive reaction of hypersensitive tissue accounts for marked exacerbations in the course of numerous allergic diseases, e.g bronchial asthma. The contributory causes of the exacerbations frequently cannot be identified no doubt psychic as well as many types of physiologic disturbances have a

part in determining the degree of hypersensitivity or the intensity of the reaction. Certainly some of the manifestations of late syphilis fit well into the category of phenomena which are commonly called allergic.

The removal of the specific antigen will stop allergic reactions. But when the antigen remains in the body as in most cases of untreated syphilis, it appears that the conflict between sensitized tissues and the syphilitic virus is not an all-out battle but a series of minor "blitzkriegs, varying in intensity and interspersed with periods of relative quiescence. During the periods of exacerbation the function of parenchymatous tissues may be impaired, only to become normal again when the exacerbation subsides, or permanent disability may result when irreparable damage has occurred

Body function and structural damage in late syphilis.—The prognosis of late symptomatic syphilis, following adequate antisyphilitic treatment, depends largely on the site and extent of permanent structural damage in body tissues. Antisyphilitic treatment destroys treponemes and so may cause dramatic improvement of symptoms in cases where the syphilitic virus interferes with the function of tissues. But killing treponemes will not replace scar tissue with functioning parenchyma.

In general paresis, appropriate therapy frequently causes remarkable improvement of mental symptoms; even in the face of widespread atrophy *in the cerebral hemispheres, but if essential centers or pathways have been* destroyed clinical improvement cannot result from treatment designed to kill treponemes. Antisyphilitic treatment can stop the further progress of primary optic atrophy but it cannot restore sight after the optic nerves have been destroyed When the lightning pains of tabes dorsalis are due to permanent demyelinization of nerve roots, and scar tissue develops, efforts to kill treponemes cannot eliminate the pains. Nor can the destruction of treponemes provide new aortic valves to patients with aortic insufficiency

Therefore, in evaluating the results of antisyphilitic treatment, we must always keep in mind the distinction between impaired function which can be restored by removing the causative agents of inflammations and impaired function which is due to scar tissue. Unless this distinction is clearly recognized considerable confusion is certain to arise in our efforts to determine the effectiveness of therapy for late symptomatic syphilis.

INFECTIOUSNESS OF LATE SYMPTOMATIC SYPHILIS

The same comments made regarding the infectiousness of latent syphilis apply to late symptomatic syphilis. In general the longer the duration

of the disease, the less infectious it is. Late syphilides of the skin are not contagious even by close contact. But we have no certain means of proving who is and who is not infectious sexually during the late stages of syphilis. The incidence of infections contracted from individuals with late syphilis is probably low but one cannot categorically deny the possibility that untreated late syphilis may rarely be infectious by sexual contact.

Similarly the blood during late syphilis is probably not infectious most of the time. Certainly the treponemes do not remain long in the blood, but they can be seeded into the blood stream from time to time and are so transferred from one site in the body to another. Thus, it is impossible to know at any given time whether or not the blood is sterile in untreated individuals during the late stages of infection.

SYPHILOPHOBIA

The story of untreated syphilis is not complete without some reference to the occasional unfortunate individuals who are obsessed with the belief that they have syphilis in spite of the fact that laboratory tests and physical examinations are completely negative for the disease. Such patients present an extremely difficult problem. They will go from physician to physician in search of treatment for their imaginary infection. If their demands for therapy are granted, they are not satisfied and wish more injections or a different type of therapy. Invariably they read everything that comes to their attention about syphilis, oftentimes gaining their knowledge from standard textbooks. The more they read the more convinced they are that they have the disease. Every ache and pain is ascribed to syphilis, and they will quote authorities to prove that negative serologic tests for syphilis do not always mean the absence of an infection. Treating such individuals for syphilis is unquestionably a mistake because such therapy probably intensifies their obsession. These persons should be treated by the psychiatrist rather than the syphilologist.

REFERENCES

Berman, H. "The Problem of Reinoculation of Human Beings with Spirocheta Pallida," *Am. J. Syph. Gonor. & Ven. Dis.* 30:173, 1946.

Brown, W. H. and Pearce, L. "The Penetration of Normal Mucous Membranes of the Rabbit by Treponema Pallidum," *Proc. Soc. Exper. Biol. & Med.*, 18:200, 1921.

Bruusgaard E. "Über das Schicksal der nicht spezifisch behandelten Luetiker" *Arch f Dermat u. Syph.* 157 309 1929

Chesney A. M. *Immunity in Syphilis,* The Williams and Wilkins Company Baltimore, 1927

——— and Kemp J "Influence of Size of Inoculum on Course of Experimental Syphilis in Rabbit," *J Exper Med.,* 41 479 1925

Dattner, B. "Probleme und Ergebnisse der Paralysebehandlung," *Klin. Wchnschr.,* 3 177 1924

——— "Evaluation of Spinal Fluid Examinations," *J Ven. Dis Inform.,* 29 63 1948

——— and Thomas E. W "The Management of Neurosyphilis," *Am. J Syph., Gonor & Ven. Dis* 26 21 1942.

Eberson F and Engman M. F An Experimental Study of the Latent Syphilitic as a Carrier" *J.A M.A* 76 160 1921

Finger, E. and Landsteiner, K. *Handb d. Geschlechtskr.,* A. Hölder Wien u. Leipzig 2 942 1912.

Fournier, A. T *aité d la Syphilis* J Rueff et Cie, Paris, 1899

Frazier, C. N and Pian H. C. "Isolation of Treponema Pallidum from the Blood during the Primary Incubation Period of Human Syphilis, *Chinese M J* 56 441 1939

Heller, J R., Jr., and Bruyere, P T "Untreated Syphilis in the Male Negro. II Mortality During 12 Years of Observation," *J Ven. Dis Inform* 27 34 1946.

Jordon J W and Dolce, F A "Latent Syphilis Study of One Hundred and Sixty-nine Cases Observed Ten Years or More," *A ch Dermat & Syph* 54 1 1946.

Kampmeier, R. H *Essentials f Syphilology* J B. Lippincott Company Philadelphia 1943

Kemp J E. "The Infectiousness of Semen of Patients with Late Syphilis. An Experimental Study" *Am. J Syph. Gonor & Ven. Dis* 22 401 1938.

Kolle. W "Über Symptomlose Infektionen und ihre Bedeutung für Epidemiologie und Immunität, insbesondere der Syphilis," *Schweiz med W hnsch* 59 517 1929

Magnuson H. J Eagle, H and Fleischman R. "The Minimal Infectious Inoculum of Spirochaeta Pallida (Nichols Strain) and a Consideration of Its Rate of Multiplication in Vivo," *Am. J Syph Gon r & Ven. Dis* 32 1 1948.

Moore, J E. *The Mod rn T atment of Syphilis* 2nd ed., Charles C. Thomas, Publisher Springfield Ill. 1942.

——— Eagle, H. and Mo re, C F A Suggested Method of Approach to the Clinical Stud of Biologic False Positive Test for Syphilis, *J A M.A* 115 1602 1940

Rich A R Pathology of 19 Cases of Nephritis Associated with Acquired Syphili " *Bull J hns Hopkins H p* 50 357 1932.

——— "Observations on the Relation of Allergy to Immunity" *Bull. J hns Hopk H p.,* 47 189 1930.

ROSAHN P D "Studies in Syphilis. VII The End Results of Untreated Syphilis," *J Ven. Dis. Inform.* 27 293 1946.
——— and BLACK-SCHAFFER, B. "Studies in Syphilis. III Mortality and Morbidity Findings in the Yale Autopsy Series," *Yale J Biol. & Med.*, 15 575 1943
SCHAMBERG I. L., and STEIGER, H. P "Syphilitic Relapse vs. Reinfection," *J Ven. Dis. Inform.* 29 91 1948.
SOWDER, W T "An Interpretation of Bruusgaard's Paper on the Fate of Untreated Syphilitics," *Am. J Syph Gonor & Ven. Dis.*, 24 684 1940
STOKES, J H. BEERMAN H and INGRAHAM N R., JR. *Modern Clinical Syphilology* 3rd ed., W B. Saunders Company Philadelphia, 1944
SYMMERS, D "Anatomic Lesions in Late Acquired Syphilis A Study of 314 Cases Based on the Analysis of 4880 Necropsies at Bellevue Hospital *J.A.M.A* 66 1457 1916.
THOMAS E. W WEXLER, G and SCHUR, M "Report of a Chancre Developing in a Patient with Cardiovascular Syphilis," *Am. J Syph. Gonor & Ven. Dis* 29 604 1945
TURNER, T B. "The Race and Sex Distribution of the Lesions of Syphilis in 10 000 Cases, *Bull. Johns Hopkins Hosp* 46 159 1930.
——— and DIESEKER, T H. "Duration of Infectivity of T Pallidum in Citrated Blood Stored under Conditions Obtaining in Blood Banks," *Bull. J hns Hopkins Hosp* 68 269 1941
URBACH, E., and BEERMAN H. "The Present Status of Immunity and Allergy in Syphilis," *Am. J Syph. Gonor & Ven. Dis.*, 31 192, 1947
USILTON L. J and MINER, J R. A Tentative Death Curve for Acquired Syphilis in White and Colored Males in the United States, *Ven. Dis. Inform.*, 18 231 1937
VONDERLEHR, R. A. CLARK, T WANGER, O C. and HELLER, J R., JR. "Untreated Syphilis in the Male Negro a Comparative Study of Treated and Untreated Cases," *Ven. Dis. I form.*, 17 260, 1936.
WAKERLIN G E. Influence of Size of Inoculum on Incubation Period and Course of Rabbit Syphilis," *J Inf et Dis.*, 38 323 1926.
WARTHIN A. S "The Persistence of Active Lesions and Spirochetes in the Tissues of Clinically Inactive or 'Cured' Syphilis," *Am. J M Sc* 152 508, 1916
——— "Lesions of Latent Syphilis," *South M J.*, 24 273 1931.

CHAPTER 3

IMMUNOLOGY OF SYPHILIS

In the preceding chapter the immunologic changes occurring during the course of untreated syphilis in man were presented. This chapter is written to summarize briefly the present knowledge of immunity in syphilis as observed in man and experimental animals.

REFRACTORY STATE TOWARD EARLY LESIONS IN MAN

It has long been established that by the time a chancre has developed, reinoculation with a few treponemes at any time during the course of untreated syphilis will not result in the development of a new chancre. This knowledge was gained in the nineteenth century when many patients received autoinoculations with homologous infectious material as well as inoculations with heterologous treponemes. Mauriac, in 1888 summarized the observations at that time as follows

1. Reinoculation (with the development of a chancre) is possible before the appearance of the chancre and during the first incubation, at least up to the twenty-second day of this period.
2. It is no longer possible when the chancre begins to develop
3. During the entire evolution of the chancre, the immunity is an accomplished fact.
4. This immunity persists in the secondary period to the same extent as in the primary period.
5. One finds it also in tertiary syphilis, and even in old syphilitic patients many years after the disappearance of every manifest lesion.
6. In very exceptional instances reinoculations have been made with success, but without the characteristic adenopathies or the cutaneous, mucous, or other lesions which always accompany the true syphilitic chancre.

To the summary given by Mauriac we can now add the following

1. The refractory state which is present by the time a chancre develops is not permanently established until after the secondary stage of

the disease has been completed. In some cases it may not be permanently established for more than 1 year after infection, but, with very rare exceptions, it is always permanently established within 2 years after infection in an untreated case.

2. Antisyphilitic treatment given during the early stages of infection interrupts the establishment of permanent "immunity" to early lesions. As a result, following unsuccessful therapy patients may relapse with infectious lesions, and, following successful therapy patients may be reinfected with the development of primary and/or secondary lesions.

Neisser insisted that the refractory state toward early lesions was not an evidence of immunity but was dependent on the persistence of foci of infection. He believed that patients cured of syphilis at any time during the course of the disease would react to reinfection with new chancres or secondary lesions. His rejection of the term immunity for the refractory state was sound only in so far as the refractory state is proof of an alteration of the reaction of tissues to the T pallidum rather than evidence of increased resistance to infection. In other words, when the refractory state toward early lesions is permanently established, the tissues are no longer capable of reacting to T pallida with lesions characteristic of the acute phase of the disease, but that does not necessarily mean an increased ability to resist T pallida. On the other hand, Neisser was mistaken in believing that cure after the first 2 years of an untreated infection would terminate the refractory state toward early lesions so that reinfection would necessarily be followed by the development of early lesions. It is not true that the best proof of cure of late syphilis is the development of a chancre when the patient is reinfected with T pallida. Whether or not a patient is cured of syphilis 2 years or more following infection, reinfection with heterologous strains of treponemes will rarely be followed by the development of early lesions, but that does not prove that the treponemes were killed by the defensive mechanism of the host because asymptomatic superinfection or reinfection may occur

REFRACTORY STATE TOWARD EARLY LESIONS IN RABBITS

In 1927 Chesney's review of the experimental data regarding the time required for the establishment of the refractory state in rabbits showed that "when the second inoculation is carried out between twenty and sixty days after the first, the percentage of successful reinoculations [with early lesions] is 78.7 when the second inoculation is performed between

the sixtieth and ninetieth day of the disease, the percentage falls to 11 4 and when it is carried out more than ninety days after the first, the percentage is 5 " * When heterologous strains were used for reinoculation, a higher percentage of reinfections with the development of chancres resulted, but the experiments of all investigators prove that the longer the time after infection when rabbits are reinoculated with heterologous strains, the more certain is the establishment of the refractory state.

The refractory state, however is not evidence of absolute immunity to reinfection in rabbits. Thus, Brown and Pearce, Chesney and Kemp, and Arnold, Mahoney and Cutler and others found that when rabbits were cured of syphilis after 90 days of infection, some could be reinfected without the development of chancres but with demonstration of treponemes in the lymph nodes. In spite of the fact that we have unsatisfactory evidence that absolute immunity to syphilis is acquired in rabbits, the available evidence indicates that a true acquired immunity in the sense of increased resistance to the infection actually occurs in rabbits.

Like human beings, rabbits vary in the degree of immunity acquired and the time when the refractory state is established. With due consideration for such variations, Magnuson, Rosenau, and Clark have recently confirmed and extended the findings of Chesney and have shown that the outcome of reinoculation following original infection in rabbits depends on two variables (1) the time at which the original infection is treated and (2) the number of treponemes inoculated. By reinoculating rabbits cured at various intervals after the original infection and by varying the number of treponemes in the inocula, these investigators came to the following conclusion

"Acquired immunity in experimental syphilis is a *continuous process* beginning as early as three weeks after the primary inoculation and increasing in degree during the first six months." †

In 1947 Arnold, Mahoney and Cutler reported on reinfections observed in rabbits which were originally treated with penicillin for latent syphilis of 8 months duration. Reinoculation of the rabbits 10 days after the completion of therapy resulted in a symptomless infection in 53 per cent, and 47 per cent were protected by the defensive factors produced by the syphilitic infection

* CHESNEY A. M *Immunity in Syphilis* The Williams & Wilkins Company Baltimore 1927

† MAGNUSON H J ROSENAU B. J and CLARK, J W JR. "The Rate of Development and Degree of Acquired Immunity in Experimental Rabbit Syphilis, paper presented at symposium held in Washington, D C Apr 17 1947 under the auspices of the Syphilis Study Section of the National Institute of Health *J Syph., Gonor & Ven. Dis* 32 418 1948.

Such experiments prove beyond all doubt that rabbits develop an increased resistance to infection which varies in degree in different animals. From clinical observations of syphilis in human beings I believe the above statement is also true of man.

SUPERINFECTION, REINFECTION AND RELAPSE

Because individuals vary in the time required to establish the refractory state toward early lesions, it is impossible to deny that syphilitic superinfection may occur with the appearance of a chancre in the presence of an already existing infection. Experimental symptomatic superinfection has been noted in human beings as well as in rabbits when large numbers of treponemes were contained in the inoculum, but symptomatic superinfection is extremely rare in naturally acquired infections. In clinical practice an absolute diagnosis of superinfection is rarely possible. Mauriac's summary of the observations on the inoculation of syphilitics in the nineteenth century indicates that the symptomatic superinfections noted were atypical and very rare. I have never seen a new chancre develop in an untreated syphilitic, and I do not believe that symptomatic superinfection, if it occurs at all in the absence of artificial inoculation with many treponemes, is a problem which demands serious consideration in clinical practice.

The distinction between infectious relapses and reinfections, however is of great practical concern. Following rapid treatment of early syphilis, the ability to distinguish reinfections from relapses would enable us to differentiate between the success and failure of the therapy given. Unfortunately we have no well-established criteria for determining reinfections in many cases.

With the advent of rapid therapy of early syphilis, the old criteria for diagnosing reinfections are no longer valid. Reinfections following rapid cure of early syphilis can occur in the presence of positive serologic tests for syphilis in both rabbits and man. At present I know of only one absolute criterion for reinfection. When a new chancre develops at a different site from the original one, I believe that a diagnosis of reinfection must be made. In such cases one must be certain that the new lesion is actually a chancre and not a secondary manifestation. A relapse of early syphilis can result in a recurrence of the original chancre (the monorecidive) Although monorecidives were not infrequently seen during inadequate and irregular treatment with weekly injections of antisyphilitic drugs, they are unusual manifestations of relapse after rapid treatment.

Unfortunately reinfections may occur in some patients treated for

early syphilis without the development of a chancre, and in such patients we have no definite criteria for distinguishing between relapses and reinfections. Many women never have demonstrable chancres after their original infection, and even more women undoubtedly do not have observed chancres after reinfection. In such cases secondary lesions are the only ones noted by either the patient or the examining physician. Also, numerous men in all probability respond to reinfection with the development of secondary lesions only When secondary lesions are the first manifestations of relapse or reinfection, we have no scientific means of differentiating between reinfection and relapse and can do no more than form *an opinion based on the history of the patient. I have always been reluctant* to make differential diagnoses between reinfections and relapses on the basis of histories, but with the passage of years I am increasingly convinced that we cannot afford to ignore histories in evaluating the results of rapid treatment of early syphilis. When patients who have received good rapid treatment of early syphilis later develop infectious lesions and give histories of exposures to known infectious cases of syphilis, the probability is that the lesions are due to reinfections rather than relapses.

The problem of differentiating reinfection from relapse will arise again in later sections of this book. In this chapter I have attempted to state the problem and to give the known facts of its immunologic background.

REINFECTION AND RELAPSE FOLLOWING TREATMENT OF LATE SYPHILIS

In late syphilis the problem of infectious lesions arises so seldom that it has little practical significance. As noted in the previous chapter I have seen a dark field positive lesion occur in only one patient after he was treated for syphilis late in the course of his infection. In all probability however patients treated after 2 years of infection can subsequently be reinfected without the occurrence of early lesions. The diagnosis in such cases is difficult, but it can be suspected in well treated patients who have had repeatedly negative serologic reactions for syphilis over many months and who later develop strongly positive tests with high reagin titers. Instances of such reversals of repeatedly negative serologic reactions to strongly positive reactions following treatment of late syphilis are infrequent, but they have been noted at Bellevue Hospital. It is also possible that a new infection may account for sustained marked increases in reagin titers which have been relatively low following treatment of late syphilis. Such sustained rises in reagin titers must usually be interpreted as either relapses or reinfections.

CONCLUSIONS

In both rabbits and man a syphilitic infection is followed by varying degrees of acquired immunity In some cases of syphilis in rabbits the immunity may be so complete that reinfection cannot occur but absolute permanent immunity against an asymptomatic syphilitic reinfection in man has not been proved. The establishment of the refractory state toward early lesions is evidence of an altered reactivity of tissues to the T pallidum and not necessarily proof of increased resistance to infection. The fact that Arnold, Mahoney and Cutler found that 47 per cent of rabbits, reinoculated with T pallida 10 days after probable cure of a latent infection, failed to develop even an asymptomatic reinfection is the best proof of acquired defensive mechanisms in the host.

When rabbits and human beings are treated for early seropositive syphilis, before the refractory state toward early lesions has become permanently established, reinfection may be followed by the development of early lesions before the serologic tests for syphilis have become negative. In other words, syphilitic reagin does not protect against reinfection, nor is there any known relationship between the amount of reagin in the blood serum and the degree of acquired immunity After a permanent refractory state toward early lesions has been established, syphilis can be cured by treatment, and reinfection may be possible without the development of early lesions. In cases of untreated syphilis, individuals vary greatly in their ability to resist infection by T pallidum and in the sensitivity of their tissues to it. Furthermore, in an individual case, the defensive mechanisms against T pallidum and the sensitivity of tissues to the microorganism vary from time to time during the course of a syphilitic infection.

In view of such observations it is not surprising that, so far it has been impossible to induce immunity to syphilis by vaccines. Not only have virulent T pallida not been cultivated, but such immune reactions as take place following a syphilitic infection require from 1 to 6 months to develop in the rabbit in man from 6 months to 2 years are usually required before even a permanent refractory state toward early lesions is established. Therefore, at the present time, the outlook for successful active immunization against syphilis is not very hopeful. Prolonged courses of vaccines would probably be necessary to produce immune reactions, and even then the existing evidence does not indicate that protection against infection would be absolute in the majority of cases. It might be possible to produce a refractory state toward early lesions by vaccines, were they available, but as the establishment of the refractory state represents the

transition from the relatively benign acute phase to the more dangerous chronic phase of the disease, attempts to use immunizing vaccines might do more harm than good.

REFERENCES

Arnold R. C. Mahoney J F and Cutler, J C "Reinfection in Experimental Syphilis in Rabbits Following Penicillin Therapy *Am. J Syph. Gonor & Ven. Dis* 31 264 1947

——— ——— and ——— "Reinfection in Experimental Syphilis in Rabbits Following Penicillin Therapy II Reinfection in Early Latent Syphilis," *Am. J Syph Gonor & Ven. Dis.,* 31 489 1947

Brown W H., and Pearce, L. "The Resistance (or Immunity) Developed by the Reaction to Syphilitic Infection and Some of the Effects of the Suppression of this Reaction, *Arch Dermat. & Syph.,* 2 675 1920.

——— and ——— Experimental Syphilis in the Rabbit. III Local Dissemination, Local Recurrence, and Involvement of Regional Lymphatics, *J Exper Med* 31 749 1920

——— and ——— "The Defensive Reactions of Animals Infected with Spirocheta Pallida, *J.A.M.A* 77 1619 1921

——— and ——— "Superinfection in Experimental Syphilis Following the Administration of Subcurative Doses of Arsphenamine or Neoarsphenamine," *J Exper Med* 33 553 1921

Chesney A. M *Immunity in Syphilis* The Williams & Wilkins Company Baltimore, 1927

——— Acquired Immunity in Syphilis," *Am. J Syph* 14 289 1930.

——— "Syphilis as a Problem in Immunity" *South. M J.,* 29 1230, 1936.

——— Holley C. R. L. and Kemp J E. "Studies in Experimental Syphilis. VII Reinoculation of Treated and Untreated Syphilitic Rabbits with Heterologous Strains of Treponema Pallidum," *J Exper Med.,* 46 223 1927

——— and Kemp J E. Studies in Experimental Syphilis. IV On Variations in the Response of Treated Rabbits to Reinoculation and on Cryptogenetic Reinfection with Syphilis, *J Exper Med* 44 589 1926.

——— and ——— "The Curability of Syphilis An Experimental Contribution, *J.A M.A.,* 88 905 1927

Levaditi C., and Levaditi, J C. Relation between Number of Treponema Inoculated and their Virulence," *Compt rend Soc de biol.,* 135 316, 1941

Magnuson H. J Rosenau B. J and Clark, J W., Jr. "The Rate of Development and Degree of Acquired Immunity in Experimental Syphilis," *J Syph., Gonor & Ven. Dis.* 32 418 1948.

Morgan H. Factors Influencing Course of Syphilis," *Am. J Syph., Gonor & Ven Dis* 25 233 1941

——— and Vryonis G "Method for Quantitation of Inocula in Experimental Syphilis, *Am. J Syph Gonor & Ven. Dis* 22 462, 1938.

NEISSER, A. *Beiträge zur Pathologie und Therapie der Syphilis*, Verlag Julius Springer Berlin, 1911

——— "Immunisierungsversuche bei der Syphilis," Arb. a. d. K., Gesdhts-amte, 37 203 1911

SCHAMBERG, I. L.: "The Effect of Early Subcurative Arsenical and Thermal Treatment on the Development of Specific Immunity in Syphilitic Rabbits," *Am. J Syph., Gonor & Ven Dis* 31 264 1947

ZINSSER, H., and HOPKINS, J G "Studies on Treponema Pallidum and Syphilis. II. Spirochetícidal Antibodies Against Treponema Pallidum," *J Exper Med* 23 323 1916.

——— ——— and McBURNEY M. "Studies on Treponema Pallidum and Syphilis. III. The Individual Fluctuations in Virulence and Comparative Virulence of Treponema Pallidum Strains Passed Through Rabbits," *J Exper Med.*, 23 329 1916.

——— ——— and ———: "Studies on Treponema Pallidum and Syphilis. IV The Difference in Behavior in Immune Serum between Cultivated Nonvirulent Treponema Pallidum and Virulent Treponemata from Lesions," *J Exper Med.*, 23 341 1916.

CHAPTER 4

INTERPRETATION OF QUANTITATIVE SEROLOGIC TESTS FOR SYPHILIS

The interpretation of serologic tests for syphilis (STS) is of paramount importance in the diagnosis of syphilis and the follow up of treated patients, and everyone concerned with the disease should know the scope and limitations of these tests. STS are not procedures for identifying the syphilitic virus but for determining the presence of a substance called reagin, which is presumably an antibody The tests are all based on techniques for identifying antibodies.

TYPES OF TESTS

The two types of STS are (1) complement fixation tests and (2) flocculation or precipitation tests.

The familiar Wassermann reaction is a complement fixation test based on the observation that complement is fixed by an antigen and its antibody Antibodies capable of hemolyzing red blood cells when complement is present will fail to hemolyze the cells in the absence of complement. Thus, in syphilis, if the unknown serum contains reagin (syphilitic antibodies) it forms antigen-antibody complex that fixes the complement consequently no complement remains free for the hemolytic (indicator) system, and hemolysis does not occur

Flocculation tests are based on the observation that reagin combines with the "antigen" used in the tests to form visible aggregates of finely divided particles. Kahn Kline, Eagle, Hinton, Mazzini, and Rein-Bossak flocculation tests are the best known in this country

"Antigen."—The "antigen" used in both the complement fixation and flocculation tests is a lipoid extract of dried beef heart. The fact that positive tests are usually specific for syphilis suggests that lipoid extracts of animal tissues, so far as laboratory procedures are concerned, have much the same antigenic activity as treponemes. Laboratory tests for antibodies, however do not have the exactness of chemical analyses, and reagin does

ot have the uniform specificity of most antibodies which can be identi-
ed in the laboratory

QUANTITATIVE STS

Quantitative STS are done to determine, more or less accurately the
mt of reagin in a serum by testing serial dilutions of the serum. The
l-point titer is not an exact measurement of the reagin, and, with the
techniques of the tests, variations in end point titers may occur
the same blood specimen when tests are made with different reagents
different days. In spite of such variations in end-point titers, quantita
STS, when repeated on the same patient at intervals over a period
months and years, afford reasonably accurate and valuable infor

Various arbitrarily selected plans of reporting end-point titers of STS
used at present. To avoid confusion it is highly desirable that a single,
iform method of reporting each type of test be adopted. At present
quantitative Kahn tests as performed by the United States Public Health
Service laboratories are reported by the formula $S = 4D$ in which S is
e potency of the serum in terms of units and D is the highest dilution
a definite precipitate. Thus, if a serum is positive in 1 4 dilu-
tion, and higher dilutions are negative, the report is 4 × 4 or 16 Kahn
units If a serum is positive in 1 8 dilution, and higher dilutions are nega
tive, the report is 4 × 8, or 32 Kahn units. For routine use the serums
tested by the United States Public Health Service laboratories are diluted
serially in doubling proportions, e.g 1 2, 1 4 1 8, 1 16 1:32, 1 64
etc. A serum giving a 4-plus reaction in the standard Kahn test and nega
tive reactions when diluted is reported as having a titer of 4 Kahn units
3-plus, 2 plus, and 1-plus standard Kahn tests are reported as 3 2, and
1 Kahn units, respectively

I am indebted to Dr Charles R. Rein for the following description of
the technique of diluting serums for quantitative flocculation tests. His
advocacy of Harris' suggestion that positive tests be reported in terms of
the highest dilution giving positive reactions seems to me worthy of uni-
versal adoption.

Dilution.—The simplest of all methods of dilution is a twofold serial
dilution which has been found to be applicable to the various types of
serologic procedures. The serum dilutions may be prepared by placing
1.0 cc of diluent in each of a series of 6 to 10 tubes. To the first tube is
added 1.0 cc of the inactivated serum. This is thoroughly mixed by draw
ing it up in the pipet several times, and then 1.0 cc of the mixture is

cell hemolysin will prevent positive complement fixation reactions in all cases but, with one exception natural sheep-cell hemolysin has not accounted for negative complement fixation tests for syphilis in patients with high Kahn titers at Bellevue Hospital. The presence of sheep-cell hemolysin in human serum can easily be determined in the laboratory In known cases of syphilis, there is as yet no explanation for marked differences between complement fixation and flocculation test titers. Such differences have been noted more frequently in patients with late syphilis than early syphilis, but it is not unusual in the follow up of patients treated for early syphilis to have one type of test become negative months before the other There is no uniformity in the discrepancies noted the complement fixation titer may remain at higher levels than the Kahn titer in some cases, or vice versa. Examples of the differences between the titers of the two tests will be shown later in this chapter

A diagnosis of syphilis cannot be made on a single positive test.—In patients with no other evidence of syphilis, it is never justifiable to make a diagnosis of syphilis on the basis of a single positive report of one type of STS. Even if two tests of the same specimen of blood are positive, another specimen should be tested before considering treatment. Serologic laboratories should be equipped to give quantitative results of at least one type of test in all cases of positive STS.

BIOLOGIC FALSE POSITIVE STS

The greater one's experience with tests of the blood serum for syphilis, the more one is convinced of the element of doubt involved in the diagnosis of syphilis solely by means of positive STS. Increasing discontent with the serologic diagnosis of syphilis has been manifested in the literature since World War II Obviously positive STS must always be correlated with careful histories and physical examinations. But it still remains true, in spite of the nonspecificity of STS that we are dependent on laboratory tests for the diagnosis of syphilis in many cases. Yaws, pinta disease, and bejel, which are due to treponemes similar to the T pallidum, cause positive STS in as high a percentage of cases as does syphilis. The reagin demonstrated in these diseases is apparently identical with that caused by syphilis. The positive STS in such cases do not belong in the same category as biologic false positive tests caused by other conditions.

Known conditions which may cause false positive STS.—Diseases which may cause false positive tests in varying but still fairly high per

centages of cases are leprosy malaria, lupus erythematosus, typhus, infectious mononucleosis, rat-bite fever Weil's disease, and brucellosis. Other conditions which may cause false positive STS are smallpox vaccination, lymphogranuloma venereum, upper respiratory infections, leukemias, and Banti's disease. Talmage, Dunn, and Breazeale reported that 35 per cent of 692 individuals wounded in battle had positive or doubtful STS. The list of conditions accused of producing false positive STS grows each year and no doubt it will continue to increase with our present sensitive tests. With the exception of the chronic diseases, most of the above conditions cause transient false positive STS lasting only a few months, and the reagin titers are usually low Among military separatees following World War II, false positive STS were noted in numerous persons who had no history or evidence of syphilis. Rosenthal and Sobel reported that only 5 per cent of 508 separatees referred to the New York City Department of Health because of positive or doubtful STS proved to have syphilis. Shaffer definitely ruled out syphilis in 43 per cent of 150 military separatees with positive STS. Such reports emphasize the necessity for great caution in making a diagnosis of syphilis on the basis of positive STS alone. In the absence of all other evidences of syphilis, patients with positive STS which might be due to other conditions should have repeated quantitative STS for at least several months before treatment is considered.

Biologic false positive STS of unknown cause.—The most annoying and baffling problem of diagnosis concerns the patient who has persistently positive STS, with normal physical findings, and no history suggestive of syphilis or of other conditions which might have caused false positive reactions. To prove that repeated positive STS in such cases are not due to syphilis is indeed difficult, but undoubtedly there are normal individuals who have biologic false positive reactions which persist for years and perhaps for life. The number of such cases is small yet for the individual involved, biologic false positive STS may be a minor tragedy and this is especially true when it appears in premarital and prenatal blood tests.

The history in such cases is of great importance and must be checked thoroughly Under the heading of "no history suggestive of syphilis," I would classify any patient who falls into one of the two following categories

1 No history of possible early lesions; no sexual exposures no evidence of congenital syphilis, either from the patient's history or from that of the parents and siblings

2 No history of possible early lesions no sexual exposures except to known individuals who have no history of syphilis and who have been examined and found to have completely negative findings for syphilis, including negative STS

When the patient fits into one of the above two categories, positive STS whether the end-point titers are high or low do not suffice to make the diagnosis of syphilis, and, in the absence of any objective evidences of the disease, I believe that a diagnosis of false positive STS should be made. Unfortunately occasional patients are seen who do not fit exactly into the above categories but still have positive tests that are probably false. In all such cases, quantitative STS should be repeated at monthly or bimonthly intervals for at least 6 months. A spinal-fluid examination should always be done. If the spinal fluid is normal and the quantitative tests remain at about the same levels (with due allowance for variations in titers caused by the variable sensitivity of the tests) a definite diagnosis of syphilis cannot be made, and the patient should be informed of that fact. Nevertheless, now that antisyphilitic treatment with penicillin can be completed within 2 or 3 weeks, it is advisable to treat such patients for possible syphilis to insure protection. If however quantitative STS, taken at intervals for at least 1 year or more following therapy show no downward trend and remain at much the same levels as before treatment, re treatment is not advisable, and the patient should be given a statement containing the pertinent facts of the case with the conclusion that the positive STS are probably biologic false positive reactions. Marked discrepancies in doubtful cases between the complement fixation and floc culation tests are suggestive of false positive reactions, but they do not rule out syphilis similarly low end point titers do not necessarily rule out syphilis, although titers of less than 4 should be regarded with great skepticism in the absence of confirmatory evidence of syphilis.

Laboratory techniques for differentiating between true and false positive STS.—Serologists have made great efforts to distinguish between reagin produced by syphilitic infection and reagin which is due to some other condition As yet, no laboratory procedures for differentiating between true and false positive STS have proved sufficiently reliable for general adoption. The most promising research on this problem has been done by Neurath at Duke University For details of the attempted differentiation between true and false positive STS, the reader is referred to the publications of Neurath and his coworkers. The findings of Neurath and his coworkers are of sufficient importance to demand further investigation

and trial. It is devoutly hoped that practical means of distinguishing be tween true and false positive STS will be forthcoming

REAGIN IN BLOOD SERUM

Reagin is contained in the globulin fractions of the serum and has at least some properties of an antibody So far as is known, however it does not confer immunity against syphilis. There is no relationship between the amount of reagin in the blood serum during a syphilitic infection and the severity of the disease. Laporte, Perez, and Hardré de Looze injected into rabbits the floccules obtained by the interaction of Meinicke s antigen and syphilitic serum and demonstrated an antibody to reagin in the blood of rabbits, thus proving that reagin has antigenic properties.

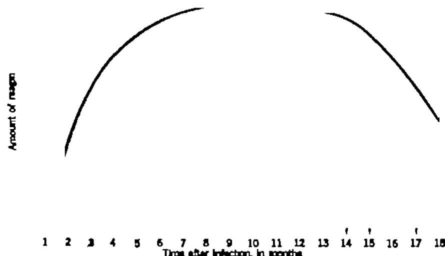


FIG. 2. Diagram of the probable curve of reagin production following infection.

When does reagin become demonstrable after infection?—In past years it was generally believed that STS did not become positive before 6 to 8 weeks after infection. It is probable, however that occasionally the tests become positive by the fourth or fifth week after infection. I have found positive STS in individuals who claimed to have had a chancre for only 1 or 2 days and who believed that they were probably infected not more than 4 or 5 weeks previously At the other extreme, in occasional instances, reagin may not become demonstrable in the blood for as long as 12 weeks after infection.

Curve of reagin production following infection.—Once reagin begins to form, it usually increases rapidly until it reaches a peak during the secondary stage. After the secondary stage has ended, as a rule, the amount of reagin in the blood decreases until it reaches a fairly stable level during the late course of the disease (Fig 2)

If early syphilis is treated while reagin is being produced in increasing amounts, a sharp rise in the titer of the quantitative STS will occur during rapid therapy of 8 or 10 days. If on the other hand, the reagin level in the blood had already reached its peak when treatment was started, there will be either no change or a slight fall in reagin titer by the end of the rapid treatment course.

Individual variations in the production of reagin.—Individuals vary greatly in their ability to produce reagin During the secondary stage of syphilis when, as a rule, the highest titers are found, Kahn titers have varied in the patients seen at Bellevue Hospital from as low as 2 to as high as 8 192 units, and complement fixation titers have varied from negative to over 1 000 Only one patient with secondary syphilis had a negative complement fixation test he had a positive Kahn test of 2 units which rose to 16 units by the end of treatment. The diagnosis of secondary syphilis was confirmed in this case by demonstrating T pallida in a papule on the face. In addition to the papular rash, he also had a penile chancre. Cases of secondary syphilis with such low titers are extraordinarily rare. In late syphilis, however it is not unusual to find low titers. Individuals with late syphilis vary in the amount of reagin formed even more markedly than those with early syphilis. The Kahn titers of patients with late syphilis observed at Bellevue Hospital have varied from 0 to 8,192 units, but the majority had titers of less than 128 units.

Negative STS in late syphilis.—At Bellevue Hospital negative STS in proved cases of active late syphilis have been found in less than 3 per cent of the patients seen in the past 10 years. It is true that the blood tests for syphilis are negative in numerous cases of tabes dorsalis, but some of the tabetics with negative blood tests represent "burned out" cases that do not have an active syphilitic process. Only 3 per cent of tabetics with evidences of syphilitic activity as demonstrated by spinal-fluid findings at Bellevue Hospital had completely negative blood tests for syphilis. Negative STS are occasionally found in patients with cardiovascular syphilis. In such cases it is difficult to determine the activity of the syphilitic process, especially in patients who have had previous antisyphilitic therapy Except in seronegative primary syphilis, negative STS are always

sufficient reason for caution in diagnosing active syphilis, but unquestionably active late syphilis may rarely be associated with negative STS

REAGIN TITERS FOLLOWING RAPID TREATMENT OF SYPHILIS

Following rapid treatment of primary or secondary syphilis, a sharp drop in reagin titers occurs within 1 month. Similarly after rapid treatment of early latent syphilis of less than 2 years duration, a relatively rapid fall in titer occurs, but the tests may not become completely negative in a high percentage of these cases for more than 1 or 2 years.

Following rapid treatment of late syphilis of more than 2 years duration, it is impossible to generalize about the fall in reagin titers, but the majority of patients treated for late syphilis do not become seronegative for at least 10 years after treatment, and many never become seronegative.

The interpretation of quantitative STS following treatment of the various stages of syphilis is extremely important. Unless the physician knows what to expect in the follow-up of patients, his management of syphilis is likely to be haphazard and oftentimes completely at fault. Therefore, the following sections on reagin titers obtained at regular intervals over long periods following treatment of the various stages of syphilis deserve special attention and study The observations reported are based on the follow-up of patients at monthly intervals for at least 2 years following rapid treatment, and at less frequent intervals thereafter

STS FOLLOWING SUCCESSFUL TREATMENT OF EARLY SYPHILIS

The purpose of this section is not to evaluate the results of various types of rapid treatment of early syphilis but to demonstrate the response of reagin titers in patients who have had successful rapid treatment of early syphilis, regardless of the kind and dosage of the antisyphilitic agents used. The rate at which patients become seronegative after successful rapid treatment does not depend on the type of therapy given but on the duration of the infection when treatment was started and on the varying capacity of different individuals to produce reagin.

Thus, seronegativity is achieved earlier by a higher percentage of patients treated for seropositive primary syphilis than for secondary syphilis. In both groups the majority of successfully treated patients at Bellevue Hospital became seronegative within 6 months, but a relatively small per

centage of patients treated for seropositive primary syphilis, and a larger percentage of those treated for secondary syphilis, failed to become seronegative for many months after treatment. In almost all cases, however successful treatment of early dark field positive syphilis produced a rapid fall in reagin titers to relatively low levels within 9 months after treatment. Thus, in general, successful treatment of seropositive primary and secondary syphilis is followed by two kinds of serologic response, which are shown in Figs. 3 and 4

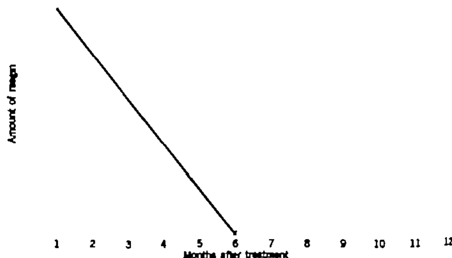


FIG. 3. Curve demonstrating rapid fall of quantitative STS to negative within 6 months after rapid treatment of early infectious syphilis.

The variations in the time required for patients to become completely seronegative after various schedules of rapid treatment of early infectious syphilis are shown in Figs. 5 to 10

A study of the tables shown in Figs. 5 to 10 clearly demonstrates that the kind of rapid treatment given, when successful does not appreciably affect the time required for patients to become seronegative following treatment. To demonstrate this fact I have chosen schedules of treatment which varied greatly in effectiveness. For example the schedule which called for only 600 000 units of amorphous penicillin was the least effective of all the rapid treatment schedules used at Bellevue Hospital, yet the patients who were cured by this schedule became seronegative in much the same manner as those treated with more effective therapy

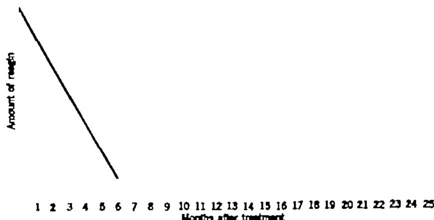


FIG 4. Curve demonstrating fall of quantitative STS to low levels which may persist for many months after rapid treatment of early infectious syphilis.

FIG. 5. PATIENTS TREATED WITH MASSIVE ARSENOTHERAPY ALONE FOR FROM 6 TO 10 DAYS (NUMBER BECOMING SERONEGATIVE EACH MONTH AFTER TREATMENT)

	Patients with Seropositive Primary Syphilis		Patients with Secondary Syphilis	
MONTHS	NUMBER	PER CENT	NUMBER	PER CENT
Within 6 months	28	82.5	77	50.3
7	1	2.9	15	9.8
8	1	2.9	9	5.9
9	2	5.9	3	1.9
10	0	0	6	3.9
11	0	0	6	3.9
12	0	0	6	3.9
Within 12 months, exact date unknown	1	2.9	10	6.6
13 to 24	0	0	7	4.6
25 to 36	1	2.9	8	5.2
37 to 48	0	0	5	3.3
49 to 60	0	0	1	0.7
	34	100.0	153	100.0

FIG. 6. PATIENTS TREATED WITH MAPHARSEN COMBINED WITH FEVERS INDUCED BY TYPHOID VACCINES (NUMBER BECOMING SERONEGATIVE EACH MONTH AFTER TREATMENT)

	Patients with Seropositive Primary Syphilis		Patients with Secondary Syphilis	
MONTHS	NUMBER	PER CENT	NUMBER	PER CENT
Within 6 months	135	78.7	355	55.2
7	3	1.8	33	5.2
8	1	0.6	32	5 1
9	1	0.6	23	3.6
10	1	0.6	24	3 6
11	2	1 1	22	3.5
12	2	1 1	18	2.8
Within 12 months, exact date unknown	21	12.0	59	9.2
13 t 24	5	2.9	39	6.0
25 to 36	1	0.6	25	3.9
37 to 48	0	0	11	1 7
49 to 60	0	0	1	0.2
	172	100.0	642	100.0

Probably a number of these patients became seronegative within 6 months.

FIG 7 PATIENTS TREATED WITH 600,000 UNITS OF AMORPHOUS PENICILLIN IN 7½ DAYS (NUMBER BECOMING SERONEGATIVE EACH MONTH AFTER TREATMENT)

	Patients with Seropositive Syphilis		Patients with Secondary Syphilis	
M NTH	NUMBER	PER CENT	NUMBER	PER CENT
Within 6 months	52	91.2	90	59 7
7	3	5 4	9	6.3
8	0	0	6	3.9
9	1	1 7	6	3.9
10	0	0	5	3.5
11	0	0	4	2.8
1	0	0	5	3.5
13 to 24	1	1 7	16	11 1
25 t 36	0	0	8	5.3
	57	100.0	151	100.0

Fifteen additional patients st ll had low quant tat e STS when last seen more than 12 months after treatment.

FIG 8. PATIENTS TREATED WITH 4,800,000 UNITS PENICILLIN IN BEESWAX AND OIL (600,000 UNITS DAILY FOR EIGHT DOSES) (NUMBER BECOMING SERONEGATIVE EACH MONTH AFTER TREATMENT)

	Patients with Seropositive Syphilis		Patients with Secondary Syphilis	
MONTHS	NUMBER	PER CENT	NUMBER	PER CENT
Within 6 months	131	92.2	142	51.3
7	1	0.7	24	8.7
8	3	2.2	13	4 7
9	2	1 4	14	5 1
10	1	0.7	10	3.6
11	0	0	15	5 4
12	0	0	15	5 4
13 to 24	4	2.8	44	15.8
	142	100.0	277	100.0

Thirty-one additional patients still had low quantitative STS when last seen more than 12 months after treatment.

FIG. 9. PATIENTS TREATED WITH 2,400,000 UNITS PENICILLIN G (40,000 UNITS EVERY THREE HOURS FOR 60 DOSES OR 26,666 UNITS EVERY 2 HOURS FOR 90 DOSES) (NUMBER BECOMING SERONEGATIVE EACH MONTH AFTER TREATMENT)

	Patients with Seropositive Primary Syphilis		Patients with Secondary Syphilis	
MONTH	NUMBER	PER CENT	NUMBER	PER CENT
Within 6 months	90	93.6	119	56.8
7	2	2.0	27	12.8
8	1	1 1	21	10.0
9	1	1 1	12	5 7
10	1	1 1	10	4.8
11	1	1.1	5	2.4
12	0	0	6	2 8
13	0	0	5	2.4
14	0	0	2	0.9
15	0	0	2	0.9
16	0	0	0	0.0
17	0	0	1	0.5
	96	100.0	210	100.0

Twenty-one additional patients still had low quantitative STS when last seen more than 12 months after treatment.

FIG. 10. PATIENTS TREATED WITH 4,800,000 UNITS PENICILLIN G (80,000 UNITS EVERY 3 HOURS FOR 60 DOSES OR 53,333 UNITS EVERY 3 HOURS FOR 90 DOSES) (NUMBER BECOMING SERONEGATIVE EACH MONTH AFTER TREATMENT)

	Patients with Seropositive Primary Syphilis		Patients with Secondary Syphilis	
MONTHS	NUMBER	PER CENT	NUMBER	PER CENT
Within 6 months	63	86.3	86	51.5
7	3	4 1	20	11.9
8	2	2 7	15	9 0
9	1	1 4	21	12.5
10	1	1 4	7	4.3
11	1	1 4	9	5 4
12	2	2.7	3	1.8
13	0	0	2	1.2
14	0	0	1	0.7
15	0	0	2	1.2
16	0	0	1	0.7
	73	100.0	167	100.0

Thirty-nine additional patients still had low quantitative STS when last seen more than 12 months after treatment.

The most important point to bear in mind regarding the fall in reagin titers following rapid treatment of early infectious syphilis is the fact that, when reagin titers have fallen to low levels within 9 months after treatment, re-treatment is unnecessary unless there are evidences of relapse or reinfection.

To illustrate the quick reversal of positive STS to negative following rapid treatment of early infectious syphilis, I have chosen two patients treated prior to the advent of penicillin, who were followed up for more than 6 years, and one patient treated with penicillin in beeswax and oil. The three examples are typical of the rapid drop in titers following any type of successful rapid therapy and they show that the height of the titer prior to treatment is not the determining factor in the rate at which positive STS become negative following treatment (Figs. 11 to 13)

The prolongation of low titers in patients treated for seropositive primary syphilis and for secondary syphilis is illustrated in Figs. 14 and 15

Discrepancies between quantitative complement fixation tests and Kahn tests following rapid treatment of early infectious syphilis.—In most cases of successful rapid treatment of early syphilis, the fall in both

FIG 11 PATIENT TREATED FOR DARK FIELD POSITIVE SEROPOSITIVE PRIMARY SYPHILIS WITH 0 06 GM MAPHARSEN DAILY FOR 10 DAYS AND FOUR FEVERS INDUCED BY TYPHOID VACCINE, JUNE 27 1941 TO JULY 6, 1941

Bellevue Hospital

DATE	COMP FIX. TITER	WASS.	KAHN
6/27/41	40	4+	4+
7 6 41	65	4+	4+
8 9 41	10	3+	4+
9 6 41	2	Neg.	Neg.
10 25 41	0	Neg.	Neg.

Seronegative thereafter t December 28, 1947 when last seen

Spinal-Fluid Examinations

DATE	WASS.	CELLS	PANDY	TOTAL PROTEIN	COLLOIDAL GOLD
6/27/41	Neg.	80/3	±	25	Normal
3 2 42	Neg.	3/3	Neg.	14	Normal
12 8 47	Neg.	4/3	Neg.	15	Normal

FIG. 12 PATIENT TREATED FOR DARK FIELD POSITIVE SECONDARY SYPHILIS WITH 0 06 GM MAPHARSEN DAILY FOR 10 DAYS AND FOUR FEVERS INDUCED BY TYPHOID VACCINE, OCTOBER 9 1941 TO OCTOBER 19 1941

Bellevue Hospital

DATE	COMP FIX. TITER	WASS.	KAHN
10/ 8/41	540	4+	4+
10 20 41	390	4+	4+
11 27 41	50	4+	4+
12 31 41	9	4+	4+
1 26 42	4	1+	3+
2 24 42	2	Neg.	Neg.
3 23 42	0	Neg.	Neg.

Seronegative thereafter to December 26, 1947 when last seen

Spinal-Fluid Examinations

DATE	WASS.	CELLS	PANDY	TOTAL PROTEIN	COLLOIDAL GOLD
5/23/44	Neg.	1/3	Neg.	14	Normal
7 31 46	Neg.	0	Neg.	16	Normal

FIG. 13. PATIENT TREATED FOR DARK FIELD POSITIVE SECONDARY SYPHILIS WITH 4,800,000 UNITS PENICILLIN IN BEESWAX AND OIL (600,000 UNITS DAILY FOR 8 DAYS) JULY 9 1946, TO JULY 17 1946

Serologic Tests Every Month After Treatment

DATE	KAHN TITER	Bellevue Hospital WASS.	KAHN
7/ 9/46	2048	4+	4+
7 17 46	1024	4+	4+
8 14 46	128	4+	4+
9 11 46	16	4+	4+
10 9 46	2	Neg.	2+
11 6 46	Neg	Neg	Neg.

Seronegative thereafter to December 26, 1947 when last seen

Spinal-Fluid Examinations

DATE	ABS.	CELLS	PANDY	TOTAL PROTEIN	COLLOIDAL GOLD
7/ 9/46	Neg.	3/3	Neg	10	Normal
12 27 47	Neg.	5/3	Neg.	14	Normal

complement fixation and Kahn titers is comparable. Occasionally one test becomes negative months before the other does. Apparently in some individuals small amounts of reagin are demonstrated better by one type of test than by the other Thus, in some cases the complement fixation test remains positive for longer periods than does the Kahn test, and in others the reverse is true. Fig 16 is an example of one type of such discrepancy

Re-treatment of patients with persistently low reagin titers following rapid treatment of early infectious syphilis.—Except for experimental purposes, at Bellevue Hospital we have not re-treated patients with persistently low reagin titers following rapid treatment of early syphilis. Sufficient numbers of patients, however were re-treated to prove to our satisfaction that re treatment does not influence the disappearance of reagin in such cases. Fig 17 illustrates failure to influence the rate at which titers fell in a patient with exceptionally prolonged positive STS following therapy

Seroresistance following rapid treatment of early infectious syphilis.—Cases of true seroresistance following rapid treatment of either seropos-

FIG. 14. PATIENT WITH PROLONGED POSITIVE STS AFTER TREATMENT OF SEROPOSITIVE PRIMARY SYPHILIS WITH 0.6 GM ARSENOXIDE AND FOUR FEVERS INDUCED BY TYPHOID VACCINE, OCTOBER 18, 1941 TO OCTOBER 27 1941

Serologic Tests

		Bellevue Hospital	
DATE	COMP FIX. TITER	WASS.	KAHN
2/18/41	170	4+	4+
2 28 41	130	4+	4+
3 18 41	56	4+	4+
3 25 41	27	4+	4+
4 22 41	26	4+	4+
5 27 41	13	3+	4+
6 24 41	13	4+	4+
7 22 41	13	4+	4+
8 19 41	14	3+	4+
9 16 41	11	3+	4+
10 14 41	10	3+	4+
11 5 41	6	2+	3+
12 3 41	6	2+	3+
12 31 41	6	±	3+
1 28 42	7	±	3+
2 25 42	7	±	3+
3 25 42	7	2+	3+
4 22 42	4	±	2+
5 24 42	5	2+	1+
6 24 42	4	±	2+
7 22 42	2	Neg.	1+
8 19 42	4	2+	2+
9 24 42	4	Neg.	2+
10 22 42	4	1+	1+
11 17 42	3	Neg.	1+
12 17 42	2	Neg.	±
1 14 43	3	±	2+
2 18 43	5	3+	2+
3 18 43	2	Neg.	±
4 28 43	2	Neg.	Neg.
6 17 43	2	Neg.	2+
10 5 43	2	Neg.	Neg.
12 15 43	3	Neg.	±
2 13 44	2	Neg.	Neg.
4 26 44	Neg.	Neg	Neg.

Seronegative thereafter to December 20, 1947 when last seen

Spinal-Fluid Examinations

DATE	WASS.	CELLS	PANDY	TOTAL PROTEIN	COLLOIDAL GOLD
2/18/41	Neg.	5/3	Neg.	16	Normal
11 10 41	Neg.	4/3	Neg.	10	Normal
11 17 42	Neg.	2/3	Neg	12	Normal
12 20 47	Neg.	1/3	Neg.	13	Normal

FIG. 15. PATIENT WITH PROLONGED POSITIVE STS AFTER TREATMENT OF PRIMARY AND SECONDARY *SYPHILIS* WITH 600,000 UNITS AMORPHOUS PENICILLIN (10,000 UNITS EVERY 3 HOURS FOR 60 DOSES) JANUARY 11 1944 TO JANUARY 18, 1944

Serologic Tests

DATE	COMP FIX. TITER	KAHN TITER
1/11/44	150	256
1 18 44	190	512
1 27 44	120	256
2 3 44	80	128
2 10 44	81	128
2 17 44	60	128
2 24 44	41	128
3 2 44	31	64
3 9 44	31	64
3 30 44	29	32
4 10 44	17	32
5 1 44	15	16
5 9 44	15	16
6 8 44	8	8
6 19 44	12	8
7 17 44	9	4
8 19 44	7	
9 12 44	5	1
10 23 44	3	1
1 18 44	4	1
2 6 45	2	Neg.
3 8 45	3	2
4 16 45	3	Neg.
5 17 45	1	Neg.
6 14 45	Neg.	Neg.
7 12 45	1	1
8 9 45	2	Neg.
9 6 45	Neg.	Neg.
10 17 45	1	Neg.
11 13 45	2	2
12 19 45	Neg.	1
2 5 46	1	1
3 8 46	2	2
6 10 46	2	1
9 12 46		1
1 13 47		1
7 1 47		Neg.
2 4 48	Neg	1

Spinal Fluid Examinations

DATE	W SS.	CELL	PANDY	TOTAL PROTEIN	COLLOIDAL GOL
9/12/44	Neg	1/3	±	21	Normal
7 21 47	Neg.	0	Neg.	18	Normal

FIG. 16. PROLONGATION OF POSITIVE COMPLEMENT FIXATION TESTS AFTER KAHN TESTS HAD BECOME NEGATIVE IN PATIENT TREATED FOR SECONDARY SYPHILIS WITH 600,000 UNITS OF *AMORPHOUS PENICILLIN (10,000 UNITS EVERY 3 HOURS FOR* 60 DOSES) NOVEMBER 29 1943 TO DECEMBER 6, 1943

DATE	COM FIX. TITER	KAHN TITER
11/29/43	320	512
12 7 43	290	512
1 3 44	69	64
2 1 44	35	16
3 2 44	19	8
3 30 44	15	2
4 13 44	11	1
5 4 44	7	0
6 8 44	5	0
7 6 44	4	0
8 13 44	5	0
9 24 44	3	0
10 13 44	0	0

Seronegative thereafter to February 6, 1948, when last seen

Spinal Fluid Examinations

DATE	WASS.	CELLS	ANDY	TOTAL PROTEIN	COLLOIDAL GOLD
11/29/43	Neg.	27/3	±	29	1110000000
8 24 44	Neg	5/3	Neg.	16	0000000000
10 25 45	Neg.	4/3	Neg.	16	0000000000
8 12 47	Neg.	6/3	Neg.	14	0000000000

tive primary or secondary syphilis are uncommon in my experience. Occasionally the reagin titers fall and then remain at relatively high levels (Kahn titers of 32 or more and complement fixation titers of 20 or more) I am confident that some of the patients at Bellevue Hospital who had Kahn titers of 64 or complement fixation titers of over 20 for a period of 6 to 9 months after treatment had actually had a serologic relapse or reinfection in the interval between examinations. When relapse or reinfection has occurred, re treatment is usually followed by a fall in reagin titers. In other cases the persistence of relatively high reagin titers represents true seroresistance and poses a difficult problem of therapy because re treatment of these cases is not, as a rule, followed by rapid drop in reagin titers. The plan adopted at Bellevue Hospital, on a more

or less arbitrary basis, is to re treat patients originally treated for early syphilis, who still have Kahn titers of 32 or more and complement fixation titers of 20 or more, 9 months after therapy If the reagin titers remain high following good re-treatment, the patient is observed at monthly intervals thereafter but unless the titers increase from previous levels or some other evidence of possible syphilitic activity appears, the per

FIG. 17 PATIENT WITH PROLONGED POSITIVE STS AFTER TREATMENT FOR PRIMARY AND SECONDARY SYPHILIS RE-TREATED 18 MONTHS AFTER ORIGINAL TREATMENT ORIGINALLY TREATED WITH 0.7 GM MAPHARSEN AND THREE FEVERS IN 7 DAYS, OCTOBER 22, 1941 TO OCTOBER 28, 1941

Serologic Tests

DATE	COMP FIX. TITER	Bellevue Hospital WASS.	KAHN	QUANTITATIVE KAHN
10/22/41	Not done	4+	4+	N t done
10 29 41		4+	4+	
11 21 41		4+	4+	
12 17 41		4+	4+	
3 18 42		4+	4+	
4 15 42		4+	4+	
5 14 4		4+	4+	
6 9 42		3+	4+	
7 8 42		4+	4+	
9 1 42		4+	4+	
9 29 42		4+	4+	
10 22 42		2+	4+	
11 19 42		+	4+	
1 14 43		±	4+	
2 4 43		Neg.	4+	
3 4 43		3+	4+	
3 18 43		4+	4+	
4 1 43		1+	4+	
4 20 43	15	1+	4+	

Spinal Fluid Examinations

DATE	W R.	CELLS	ANDY	TOTAL PROTEIN	COLLOIDAL GOLD
10/22/41	Neg.	1	Neg.	10	Neg.
6 9 42	Neg.	1	Neg	12	Neg
4 21 43	Neg.	1	Neg.	12	Neg

FIG. 17 (*Cont'd*)

RE-TREATED WITH 0.84 GM MAPHARSEN AND FOUR FEVERS IN 10 DAYS, APRIL 26, 1943 TO MAY 5 1943

Serologic Tests

DATE	COM. FIX. TITER	Bellevue Hospital WASS.	KAHN	QUANTITATIVE KAHN
4/26/43	13	±	4+	Not done
5 6 43	8.5		4+	
6 1 43	11		4+	
7 1 43	14	2+	4+	
7 29 43	10	+	4+	
8 26 43	14	4+	4+	
9 23 43	24	4+	4+	
10 21 43	13	+	4+	
11 18 43	14	+	4+	
12 16 43	10	+	4+	
1 13 44	8.5	3+	4+	
2 10 44	10	+	4+	
3 2 44	9	+	4+	
4 27 44	10	Neg.	4+	
8 3 44	8.2	Neg.	4+	
11 16 44		Neg.	4+	
2 15 45		Neg.	4+	
8 23 45		Neg.	4+	
2 7 46		Neg.	4+	
2 14 46	3		4+	16
3 28 46		Neg.	4+	8
8 29 46	3		3+	3
2 13 47	2		3+	3
1 29 48	2		Neg.	0

Spinal-Fluid Examinations

DATE	WASS.	CELLS	ANDY	TOTAL PROTEIN	COLLOIDAL GOLD
4/21/43	Neg.	1	Neg.	12	Neg.
3 2 44	Neg.	2	Neg.	10	Neg.
2 14 46	Neg.	1/3	Neg.	12	Neg.

sistence of positive STS is not considered an indication for further antisyphilitic therapy In such cases, the spinal fluid should always be examined If positive tests for syphilis are found in the spinal fluid, re treatment is, of course, indicated.

Does the prolongation of low reagin titers for many months after treatment of early syphilis mean the continued presence of foci of infection?—For the following reasons, I believe the answer to this question is in the negative

1 The patients with prolonged low reagin titers following rapid treatment of early syphilis at Bellevue Hospital have finally become seronegative unless they relapsed or were reinfected

2 Re treatment failed to influence the rate at which such patients became seronegative.

3 If low reagin titers for periods of 20 months or more following treatment of dark field positive syphilis were due to foci of infection, patients with such titers should establish a permanent refractory state toward early lesions. Such a refractory state failed to occur in 9 patients who had positive STS for more than 20 months following rapid treatment of early syphilis at Bellevue Hospital as proved by the fact that they subsequently had infectious relapses or were reinfected and developed dark field positive lesions before the STS became completely negative.

4 If the prolonged presence of relatively small amounts of reagin in patients treated for early syphilis represented foci of infection (which were finally eliminated by the defenses of the host) we would expect to see more such persistent low-titered serologic tests in patients treated by poor schedules than by good schedules. Yet the percentage of patients with prolonged positive STS who failed to relapse or be reinfected following poor schedules of therapy was approximately the same as that following much more effective treatment. (See Figs. 5 to 10)

REAGIN TITERS IN RELAPSE OR REINFECTION FOLLOWING RAPID TREATMENT OF EARLY SYPHILIS

Both relapse and reinfection following rapid treatment of early syphilis will cause marked and sustained rises in reagin titers from previous levels. In cases of reinfection new primary lesions may appear before the reagin increases, but infectious relapse, in my experience, has always been associated with serologic relapse. In some instances the only demonstrable evidence of relapse is a serologic relapse. Consequently quantitative STS are essential in the follow-up of patients who have had rapid treatment of early syphilis. Occasionally fluctuations in titer as a result of technical variations and other factors, may give a false impression of relapse. Therefore, the diagnosis of serologic relapse should not be made on the basis of

FIG. 18. RELAPSE OR REINFECTION OF PATIENT TREATED FOR SECONDARY SYPHILIS WITH 600,000 UNITS OF PENICILLIN (10,000 UNITS EVERY 3 HOURS FOR 60 DOSES) JUNE 7 1944, TO JUNE 15 1944

Serologic Tests

DATE	COMP FIX. TITER	KAHN TITER
6/ 7/44	99	128
6 15 44	40	64
7 3 44	29	32
7 29 44	15	32
9 21 44	5	3
11 4 44	Not done	16
12 6 44	12	16
12 18 44	29	32
12 28 44	58	64
1 4 45	53	64

Spinal Fluid Examinations

DATE	WASS.	CELLS	PANDY	TOTAL PROTEIN	COLLOIDAL GOLD
6/7/44	Neg.	1/3	Neg.	15	Normal
1 4 45	Neg.	3/3	Neg.	15	Normal

PATIENT RE-TREATED WITH 2,400,000 UNITS PENICILLIN (40,000 UNITS EVERY 3 HOURS FOR 60 DOSES) JANUARY 4, 1945 TO JANUARY 13 1945

Serologic Tests

DATE	COM FIX. TITER	KAHN TITER
1/ 4/45	53	64
1 13 45	44	64
3 8 45	Not done	16
4 9 45		3
6 11 45		3
11 17 45		8
1 19 46		8
2 28 46		3
3 1 46	Neg.	3
4 23 46	Not done	3
6 19 46		3
11 7 46	Neg.	Neg.

Seronegative thereafter until December 17 1947 when last seen

FIG 19. RELAPSE OR REINFECTION OF PATIENT TREATED FOR SECONDARY SYPHILIS WITH 4,800,000 UNITS PENICILLIN IN BEESWAX AND OIL (600,000 UNITS DAILY FOR 8 DAYS) JANUARY 8, 1946, TO JANUARY 15 1946

Serologic Tests

DATE	KAHN TITER	Bellevue Hospital WASS.	Bellevue Hospital KAHN
1/ 8/46	1024	4+	4+
1 16 46	2048	4+	4+
2 13 46	256	4+	4+
3 19 46	3	4+	4+
5 8 46	3	Neg.	2+
6 10 46	Neg	Neg.	Neg.
7 11 46	Neg	Neg.	Neg.
8 14 46	Neg	Neg.	Neg.
9 16 46	3	1+	2+
10 7 46	64	4+	4+
11 12 46	128	4+	4+

Spinal Fluid Examinations

DATE	WASS.	CELLS	ANDY	TOTAL PROTEIN	COLLOIDAL GOLD
1/ 8/46	Neg.	1/3	Neg.	12	Normal
11 12 46	Neg	21/3	Neg.	18	2110000000

PATIENT RE-TREATED WITH 4,800,000 UNITS PENICILLIN IN BEESWAX AND OIL, NOVEMBER 13 1946, TO NOVEMBER 21 1946

Serologic Tests

DATE	KAHN TITER	Bellevue Hospital WASS.	Bellevue Hospital KAHN
11 12 46	128	4+	4+
11 21 46	128	4+	4+
12 20 46	128	4+	4+
1 22 47	64	4+	4+
2 24 47	16	4+	4+
3 27 47	3	1+	2+
4 24 47	3	Neg.	+
6 2 47	1	Neg	Neg.
7 3 47	Neg.	Neg	Neg.

Remained seronegative thereafter to January 20, 1948, when last seen

Spinal Fluid Examination

DATE	WASS.	CELLS	ANDY	TOTAL PROTEIN	COLLOIDAL GOLD
6/2/47	Neg	2/3	Neg.	12	Normal

a single test showing a rise in titer If, however repeated tests reveal a definite, sustained rise in titer from previous levels, re-treatment is necessary Examples of serologic relapse are shown in Figs. 18 and 19

Do quantitative STS help in distinguishing between relapses and re infections?—When a chancre develops in a patient who has had rapid treatment of early syphilis, before the reagin titers have increased from previous levels, the most likely diagnosis is reinfection. This statement is true whether or not the STS have become negative following rapid treat ment. In all other cases the relationship between the time when infectious lesions appear and the time when increased reagin titers are noted is of no proved value in distinguishing between relapses and reinfections.

I once believed that serologic relapse preceding the appearance of early lesions was evidence in favor of relapse rather than of reinfection. How ever a careful review of the relapses and reinfections observed at Bellevue Hospital has made me less certain of this opinion. Too many variables enter into the analysis of such cases to permit a final conclusion that increase of reagin titer before lesions are noted invariably indicates relapse and not reinfection. Often patients who were probably reinfected return with secondary syphilitic lesions only not having had, or noted, a chancre. Positive STS always precede the appearance of secondary syphilitic lesions, in my experience, and, therefore, increases in titer will be present in cases of reinfection prior to the development of secondary lesions.

It might be expected that the STS would become negative more rapidly following re-treatment of a reinfection than of a relapse, but here again individual variations in formation of reagin are so great that no definite criterion for differentiating between relapse and reinfection can be established on this basis.

As a matter of fact, the stimulus to the formation of reagin is much the same in relapse and reinfection In relapse a few treponemes which have been dormant within the body begin to multiply and stimulate the formation of reagin, while in reinfection the same process occurs, with the exception that treponemes have entered the body from outside. In either case the formation of reagin is much the same, and it has not been shown that the heterologous treponemes in a reinfection have an effect different from that of the homologous treponemes in a relapse. I do not believe that quantitative STS are of much help in differentiating between relapse and reinfection, except in cases of reinfection where a chancre appears before the reagin titer shows an increase from previous levels. Rein, however in an article on "The Serologic Tests in Penicillin-treated Syphilis," has pointed out that if patients were subjected to serologic

examinations at weekly intervals, a rise in the titer of the quantitative tests prior to the appearance of lesions would probably be of value in differentiating relapse from reinfection in many cases.

REAGIN TITERS FOLLOWING TREATMENT OF EARLY LATENT SYPHILIS OF LESS THAN 6 MONTHS' DURATION

Reagin titers following rapid treatment of early latent syphilis of less than 6 months duration drop rapidly in much the same manner as following rapid treatment of secondary syphilis. About 65 per cent of the patients treated at Bellevue Hospital for early latent syphilis of less than 6 months' duration became seronegative within 1 year after treatment, and an additional 20 per cent became seronegative or had very low reagin titers within 2 years after treatment.

EARLY LATENT SYPHILIS OF FROM 6 MONTHS' TO 2 YEARS DURATION

Of the patients given rapid treatment at Bellevue Hospital for latent syphilis of from 6 to 24 months duration only about 40 per cent became seronegative within 2 years after treatment, and the reagin titers frequently remained at higher levels for a longer period than in the case of patients treated for early syphilis of less than 6 months' duration.

REAGIN TITERS FOLLOWING RAPID TREATMENT OF LATE SYPHILIS OF MORE THAN 2 YEARS DURATION

After 2 years of infection, patients vary greatly in the manner in which their quantitative STS respond to treatment and they also vary greatly in the time required for the STS to become negative. Some patients have had marked decreases in reagin following rapid treatment of late syphilis, and others have not. As long as the trend of reagin titers following rapid treatment of late syphilis was downward and there were no pronounced, sustained rises in titers from previous levels, re-treatment has not hastened the reversal of positive STS to negative. At Bellevue Hospital we have found that malaria, artificial hyperpyrexia, arsenical drugs, and penicillin have had no appreciable effect in reversing positive STS to negative in patients who had had adequate previous therapy.*

In view of the large number of requests to treat patients at the Bellevue Hospital Rapid Treatment Center solely because of persistently positive

* Charts showing the serologic response to various types of antisyphilitic treatment for late latent syphilis will be found in Chap. 10.

STS after much previous therapy for late syphilis, it is important for those concerned with the management of syphilis to recognize that the main purpose of treatment of late syphilis is not to obtain negative STS but to arrest whatever active syphilitic process may be present. In 70 to 80 per cent of cases of late syphilis, no amount and kind of additional treatment will reverse positive STS to negative within 5 years. But the percentage of patients who become seronegative in a given time after treatment of late syphilis is of small significance the important question is

Do quantitative STS in the follow-up of patients treated for late syphilis give any clue to the activity of the infection?—The answer to this question is subject to numerous qualifications, but, in general, I have found quantitative STS of value in the follow-up of patients treated for late syphilis. In spite of frequent fluctuations in the reagin titers, the trend is usually downward following treatment of late syphilis. A marked rise in titer from previous levels, which persists or continues to rise for several months and cannot be ascribed to any other known cause, is probably an indication of renewed activity of the infection, or of reinfection. It must be clearly understood, however that the height of a single titer in any given case of syphilis has no relationship to the severity of the disease or the degree of activity Only marked, sustained rises in titers from previous levels have significance in the follow-up of patients treated for late syphilis. Patients treated for neurosyphilis may show evidence of relapse in the spinal-fluid tests without significant changes in the titers of the blood serum. Figure 20 however illustrates a relapse in a patient treated for late neurosyphilis, with evidences of serologic relapse in both the spinal fluid and blood. A case such as this demonstrates that it is impossible to ignore marked rises in blood titers in the follow-up of patients treated for late syphilis.

Definition of marked, sustained rises in STS titers from previous levels following treatment for late syphilis.—It is difficult to define in exact terms my conception of what constitutes a marked, sustained rise in STS titers in patients who have been treated for late syphilis. When the titers have been relatively low (complement fixation titers of 10 or less or quantitative Kahn tests of 16 or less) a rise of even 100 per cent is not significant. Some patients may even have negative tests at times and titers of 1 to 4 at other times without having significant changes in the reagin content of the blood. Rises in complement fixation titers from 20 to 40 or quantitative Kahn tests from 8 to 32, sustained for several months,

FIG. 20. SEROLOGIC RELAPSE, AS DEMONSTRATED BY BOTH BLOOD AND SPINAL-FLUID TESTS, IN PATIENT TREATED FOR LATE ASYMPTOMATIC NEUROSYPHILIS WITH 6,000,000 UNITS OF PENICILLIN (40,000 UNITS EVERY 3 HOURS FOR 150 DOSES) JANUARY 14 1946, TO FEBRUARY 2, 1946

	Blood STS		Spinal-Fluid Examinations				
DATE	COMP. FIX. TITER	KAHN TITER	COMP. FIX. TITER	CELLS	PANDY	TOTAL PROTEIN	COLLOIDAL GOLD
1/14/46	160	128	13	35/3	Neg.	28	9,12,14,9,8,6,5.5,..,5,1(69)
2 46	150	256					
3 7 46	110	128					
4 4 46	77	32					
5 2 46	57	8	5	5/3	Neg.	22	8.5,9.5 13,8.5,8,7,5,3.5,2.5,1(67)
6 6 46	39	32					
7 10 46	Not done	16					
9 17 46	37	16	6	4/3	Neg.	24	7,8.5,8,8,7.5,6,5,3 1.5 1(55)
11 21 46	37	16					
6 23 47	150	128	30	66/3	1+	30	11 14 13,10,9 7.5,6,5,3,..(81)
7 18 47	150	128					

FIG. 21. FLUCTUATIONS IN STS TITERS FOLLOWING TREATMENT OF PATIENT WITH ASYMPTOMATIC NEUROSYPHILIS (INCREASED CELLS IN SPINAL FLUID) WITH 3,200,000 UNITS OF PENICILLIN (40,000 UNITS EVERY 3 HOURS FOR 80 DOSES) DECEMBER 21 1945 TO DECEMBER 31 1945

Serologic Tests E ery Month After Treatment

DATE	COM FIX. TITER	KAHN TITER
12/21/45	62	2
12 31 45	60	1
2 2 46	70	0
3 2 46	72	4
3 30 46	73	0
4 27 46	70	4
5 25 46	84	1
6 20 46	70	1
7 18 46	64	1
8 15 46	50	4
9 12 46	56	0
10 10 46	69	0
11 7 46	96	64
12 2 46	Not done	32
7 10 47	55	0
8 25 47	61	0
12 4 47	35	0

Spinal-Fluid Examinations

DATE	WASS.	CELLS	ANDY	TOTAL PROTEIN	COLLOIDAL GOLD
12/21/44	Neg.	340/3		52	Not done
10 10 45	Neg.	2/3	Neg.	19	4,5,5,5,5 4,3,2, 1 5,3,,5 (31)
12 4 47	Neg.	2/3	Neg.	20	5 7 7,6,5,5 5 4 3,2,,5,0(41)

may be significant, although in such cases the titers of both types of tests should show a sustained rise for at least 3 months before they can be regarded as suggestive of renewed activity of a syphilitic infection, regardless of whether the renewed activity is due to reinfection or relapse. Serologic relapses in well-treated patients for late syphilis are relatively uncommon, and, when they occur the titers usually show an increase with each successive test taken at intervals of 2 weeks or more. Steady increases m the titers of both types of tests, e.g., complement fixation tests which

FIG. 22. FLUCTUATIONS IN STS TITERS FOLLOWING TREATMENT OF PATIENT WITH CARDIOVASCULAR SYPHILIS (AORTIC INSUFFICIENCY) WITH 4,000,000 UNITS OF PENICILLIN (40,000 UNITS EVERY 3 HOURS FOR 100 DOSES) PATIENT GAVE HISTORY OF HAVING HAD 20 MONTHS OF REGULAR WEEKLY TREATMENT WITH ALTERNATE COURSES OF BISMUTH AND MAPHARSEN STARTING JULY 1943 TREATED WITH PENICILLIN AT BELLEVUE HOSPITAL APRIL 26, 1945 TO MAY 9 1945

Serologic Tests Every Month After Treatment

DATE	COMP FIX. TITER	KAHN TITER
4/24/45	97	128
5 9 45	120	128
6 4 45	110	256
7 12 45	96	128
8 6 45	90	256
9 5 45	95	256
10 3 45	80	256
11 30 45	93	256
12 28 45	68	32
1 25 46	87	128
3 1 46	110	128
3 29 46	79	64
5 28 46	56	128
6 24 46	84	128
7 25 46	Not done	64
8 29 46		128
7 26 46	56	32
10 4 46	68	Not done
11 1 46	84	128
1 9 47	80	128
2 6 47	Not done	128
3 6 47	64	128
4 10 47	76	128
5 8 47	85	64
6 12 47	63	128
9 4 47	90	64
11 20 47	52	64

show increases at biweekly intervals such as 20 40, 60 80 and Kahn titers with increases such as 16 32 64 128 presumably indicate a renewed activity of the infection, unless some other cause than syphilis can be found for the increase in the reagin content of the blood. Transient fluctuations in titers, even when very marked, are not indications for re-treatment.

FIG. 23. MARKED DISCREPANCY BETWEEN COMPLEMENT FIXATION TESTS AND KAHN TESTS IN PATIENT WITH NO DEFINITE HISTORY OF SYPHILIS BUT WHO HAD FREQUENT PROMISCUOUS EXPOSURES AND WAS TREATED FOR GONORRHEA WITH PENICILLIN, OCTOBER, 1945. SYPHILIS CANNOT BE PROVED IN THIS CASE BUT SEEMED PROBABLE. THIS CASE ALSO ILLUSTRATES MARKED FLUCTUATIONS IN KAHN TITERS FOLLOWING TREATMENT. PATIENT TREATED FOR SYPHILIS WITH 4,000,000 UNITS PENICILLIN (40,000 UNITS EVERY 3 HOURS FOR 100 DOSES) JANUARY 31 1946, TO FEBRUARY 13 1946

Serologic Tests Every Month After Treatment

DATE	COMP. FIX. TITER	KAHN TITER
1/31/46	Neg.	128
2 13 46	Neg.	128
3 30 46	Neg.	64
5 1 46	Neg.	256
5 27 46	Neg.	32
7 12 46	Neg.	8
8 21 46	Neg.	16
9 28 46	Neg.	64
11 11 46	Neg.	16
12 12 46	Neg.	1
2 3 47	Neg.	3
3 18 47	Neg.	3
4 30 47	Neg.	0
6 24 47	Neg.	0
8 14 47	Neg.	3
10 7 47	Neg.	0

Spinal-Fluid Examinations

DATE	WASS.	CELLS	PANDY	TOTAL PROTEIN	COLLOIDAL GOLD
1/31/46	Neg.	6/3	±	19	Normal
6 24 47	Neg.	2/3	Neg.	18	Normal

Fluctuations in reagin titers following rapid treatment of late syphilis.—As previously noted, fluctuations in reagin titers are frequently due to the varying sensitivity and techniques of laboratory tests, but this explanation cannot account for marked fluctuations in titers noted in occasional patients. If laboratory techniques alone were the cause of the marked variations in titers noted over many months, we would expect similar

FIG. 24 MARKED DISCREPANCY BETWEEN COMPLEMENT FIXATION TESTS AND KAHN TESTS IN PATIENT WITH NO DEFINITE HISTORY OF SYPHILIS. HE HAD HAD FREQUENT PROMISCUOUS EXPOSURES AND TWO GONORRHEAL INFECTIONS. SYPHILIS CANNOT BE PROVED IN THIS CASE BUT SEEMED PROBABLE. TREATED FOR SYPHILIS WITH 3,200,000 UNITS OF PENICILLIN (40,000 UNITS EVERY 3 HOURS FOR 80 DOSES) AND FIVE INJECTIONS OF BISMUTH SUBSALICYLATE 0.2 GM EACH MAY 7 1947 TO MAY 17 1947

Serologic Tests Every Month After Treatment

DATE	COMP FIX. TITER	KAHN TITER
5/ 7/47	30	Atypical ±
5 17 47	27	Neg.
7 1 47	4	2
8 11 47	32	Neg.
9 29 47	26	3
10 27 47	33	Neg.
12 19 47	29	2

Spinal Fluid Examination

DATE	WASS.	CELLS	PANDY	TOTAL PROTEIN	COLLOIDAL GOLD
5/8/47	Neg.	5/3	Neg.	10	Normal

fluctuations in many patients, yet marked fluctuations and discrepancies in titers determined at monthly intervals have been observed only in a minority of cases at Bellevue Hospital. Evidently some serums are more subject to variations in titers than others. This observed fact may not be due to actual variations in the amount of reagin in the blood serum It is possible that other unknown factors in the serums of these patients make it difficult to determine accurate end-point titers. Whatever the explanation may be, fluctuations in STS titers are not indications for re-treatment. The fact that they occur emphasizes the need for repeated quantitative STS before concluding that a patient has had a serologic relapse. Examples of unusual fluctuations and discrepancies in titers are given in Figs. 21 and 22

Discrepancies between complement fixation titers and Kahn titers in late syphilis.—By marked discrepancies between complement fixation

titers and Kahn titers I mean relatively high titers with one of the tests and low titers or negative reactions with the other A Kahn test of 512 units and a complement fixation titer of 100 would not be a marked discrepancy because both titers are relatively high, but a Kahn titer of 256 or 128 and a complement fixation titer of 10 or less, or vice versa, would be a marked discrepancy Such discrepancies in known cases of syphilis have been observed occasionally at Bellevue Hospital. The reason for the discrepancies is unknown. In cases where syphilis cannot be proved, marked discrepancies, especially positive reactions with one type of test and negative reactions in the other suggest false positive rather than syphilitic reactions. Examples of marked discrepancies between the two types of tests in unproved but probable syphilis are shown in Figs. 23 and 24.

REASONS FOR PERSISTENT POSITIVE STS FOLLOWING RAPID TREATMENT OF LATE SYPHILIS

In a previous section of this chapter I gave reasons for believing that the persistence of low reagin titers for many months following rapid treat ment of early syphilis does not indicate the continued presence of foci of infection. Neither does the persistence of reagin in patients treated for late syphilis necessarily mean the persistence of foci of infection, in my opinion. The fact that STS remain positive for much longer periods fol lowing treatment of late syphilis than of early syphilis does not in any way detract from the conclusion that positive STS following treatment of late syphilis do not necessarily indicate foci of infection. Scientific proof of this belief is not available, but clinical observations favor it and there are also good theoretical reasons for believing that the presence of reagin in the blood serum following treatment is not necessarily evidence of a continued syphilitic infection.

In the laboratory at least, reagin behaves like an antibody and we know that individuals vary greatly in the antibodies formed and in the length of time antibodies are demonstrable after an infection or after immunizing vaccines. For example, injections of dead typhoid bacilli will cause the production of agglutinins for Bacillus typhosus. Following a series of typhoid-vaccine injections, most individuals will have positive Widal's tests, but the amount of agglutinins demonstrable varies in dif ferent individuals as does the length of time during which positive Widal's tests are found. Yet it would not occur to anyone to confuse a positive Widal's test in such cases with foci of B typhosus infection.

In late syphilis the body cells have had ample time to acquire the habit

of forming reagin, and it is theoretically possible that reagin continues to be formed for many years after the infection has been eliminated. In treated cases of syphilis it is impossible to know if all treponemes have been destroyed by the treatment. Therefore, patients treated for late syphilis should be observed as long as possible, but unless there is clinical evidence of progression or definite serologic relapse, re treatment is unnecessary merely because the STS remain positive. Patients who have been well treated for late syphilis should always be instructed that positive STS do not necessarily mean the continued presence of syphilis. Much unnecessary anxiety has been caused in the past by failing to give this

FIG 25. SUMMARY OF QUANTITATIVE STS AND INDICATIONS FOR RE-TREATMENT

1 In primary and secondary syphilis, successful rapid treatment is followed in the majority of cases by negative serologic tests for syphilis within 6 months.

2. Patients with negative spinal-fl ld findings but persistently low blood STS titers for more than 1 year after rapid treatment of primary or secondary syphilis req ire no further therapy unless marked sustained rises in STS titers occur

3 P tient treated for primary and secondary syphilis who develop new infec tious lesions or have definite sustained rises in STS titers at any time after rapid treatment should be re treated.

4 Patients treated for primary or secondary syphilis, who continue to have complement fixation titers f 20 or greater or quantitative flocculation tests of 3 or greater 9 months after rapid therapy may be re-treated as precautionary measure.

5 P tients given rapid treatment of early latent syphilis of less than 6 months duration may be expected t become seronegative within 1 year after treatment in th majority of cases. The persistence of low STS titers in such patients for more than 1 year is not an indication for further treatment.

6. Patients with latent syphill of more than 6 months duration as rule require more than 1 yea to become completely seronegative. I general, the longer the duration of latent syphilis, p to 2 years, the longer the time equired for the STS t become negative. Re treatment is not indicated in such patients unless the f llow-up STS titers show definite and sustained rises from previous levels.

7 The primary aim of treatment in lat latent or lat symptomatic syphilis of more than years duration is not to obtain negative STS but to heal ctive lesions and prevent further progress of the disease. The failure to reverse positiv STS t egard in such cases does not necessarily mean the persistenc of foci of infection.

8. Some patient ma ha marked fluctuations i STS titers during the years following treatment of lat syphill Such fluctuation can be disre garded If however marked rises in STS titers occur which are sustained for 3 months, further investigation for evidence of relapse is indicated, and re treatment i generally dvisable.

nformation to treated patients. Well-treated patients who still have posi tive STS should not be regarded as infectious in any way merely because of the persistence of positive STS.

SPINAL-FLUID TESTS IN SYPHILIS

At least four different tests should be done routinely in examining the spinal fluid for evidences of a syphilitic infection in the central nervous system (1) quantitative complement fixation reaction, (2) cell count, (3) total protein determination, and (4) colloidal test.

QUANTITATIVE COMPLEMENT FIXATION TEST

Titrated complement fixation tests for reagin in the spinal fluid can be done by much the same technique as can complement fixation titers for reagin in blood serum. The New York State Department of Health laboratory has provided the Syphilis Service at Bellevue Hospital with such tests for the past 3 years. We have found reports of spinal-fluid reagin in units more helpful than the older method of reporting positive Wassermann reactions in varying amounts of fluid. Fluctuations in spinal-fluid reagin titers are less frequently observed than in titers of reagin in the blood. The amount of reagin in the spinal fluid, as in the blood, is no indication of the severity of the syphilitic infection, but the drop in spinal-fluid reagin titers following treatment is usually more rapid and con tinuous than in the case of the blood.

False positive tests.—Complement fixation reactions for reagin in the spinal fluid are much more specific than in the blood false positive tests have been reported and undoubtedly have occurred, but they have been very rare in our experience at Bellevue Hospital.

Relationship between reagin in the blood and spinal fluid.—Reagin is formed independently in the blood and spinal fluid. There is no rela tionship between the amount of reagin in the blood and the amount in the spinal fluid. In pathologic conditions which cause increased perme ability of the blood vessels, serum containing reagin may enter the spinal fluid from the blood. Such conditions are uncommon among them, acute meningitis and arsenical encephalopathy might be mentioned.

CELL COUNTS

Accurate cell counts are of great importance in spinal-fluid examina tions for syphilis. On the basis of our experience with more than 35 000 spinal fluids examined at Bellevue Hospital, I am convinced that any number of cells greater than 4 per cubic millimeter is abnormal. Various counts up to as high as 8 per cubic millimeter have been regarded as normal by numerous workers in syphilis, but there is good authority in

the literature for regarding more than 4 cells per cubic millimeter as abnormal. Among those who consider 4 cells to be the upper limit of normal are Dattner Neel, Brain, Boyd, Greenfield and Carmichael, and Merritt and Fremont-Smith.

Cell counts should be made with large counting chambers which will permit the cells in at least 3 cu mm to be counted. The Fuchs-Rosenthal chamber is preferred. If the cells in all of the ruled spaces of this chamber are counted, the result will be the number of cells in 3 cu mm fluid. The report should then be made in thirds. Thus, a count of 15 cells in the Fuchs-Rosenthal chamber would be reported as 15/3

When done with care, cell counts are one of the most sensitive and valuable guides to the activity of a syphilitic process in the central nervous system At Bellevue Hospital increased cell counts have been found in most of the previously untreated patients with neurosyphilis.

TOTAL PROTEIN DETERMINATIONS

The only exact method of determining the amount of protein in the spinal fluid is Kjeldahl's method which is too difficult for routine use. However exactness in terms of the actual milligrams of protein in each cubic centimeter of spinal fluid is less important in syphilis than fairly accurate approximations which are consistent and comparable. Turbidity tests afford adequate information about the amount of protein in the spinal fluid provided the degree of turbidity is determined with an electrophotometer and not by readings taken with a colorimeter At Bellevue Hospital total protein determinations are made by adding 1 cc Exton's protein reagent to 1 cc spinal fluid and reading the degree of turbidity in an electrophotometer after the mixture has stood for 10 minutes. The upper limit of normal with this method is 35 mgm per cent.

Colloidal reactions.—Within recent years Lange has greatly improved his original colloidal gold test so that it gives quantitative as well as qualitative information. The variations in color in the 10 tubes of the test are no longer numbered from 0 to 5 but from 1 to 20 By adding the color numbers in all 10 tubes, a quantitative report is made. Normally the 10 tubes should not add to more than 45 The highest possible total reading would be 200 a result which I have never seen but not infrequently the spinal fluid of patients with general paresis has had a quantitative colloidal gold reading of 180 with readings of 18 in each of the 10 tubes. As with the older more familiar colloidal tests, first zone curves, in which the highest figures occur in the first few tubes, or curves in which high figures are reported in all of the tubes, represent parenchymatous damage

in the central nervous system. Such curves are commonly seen in general paresis but may be found in any type of neurosyphilis, including asymptomatic involvement of the central nervous system. Syphilis is not the only cause of abnormal colloidal curves, but, in the absence of other causes and in association with specific tests for syphilis, abnormal colloidal curves must be attributed to syphilitic infection of the central nervous system.

Qualitative tests for increased protein.—In addition to the four essential tests of spinal fluid which have been described, a qualitative test for increased protein is useful. A Pandy test can be done during the withdrawal of spinal fluid by permitting 5 drops of fluid to fall into 1 cc Pandy solution. If the solution becomes turbid immediately the test is positive.

SPINAL-FLUID SYNDROME

The above tests of the spinal fluid, taken together form a pattern which yields essential information in the management of neurosyphilis. Syphilitic activity in the central nervous system is indicated by increased cells which are definite evidence of inflammation. In untreated patients with neurosyphilis, increased protein in the spinal fluid is again evidence of syphilitic activity. Abnormal colloidal gold curves reflect a pathologic process in the central nervous system, and in association with the other tests they are of value. The first zone curve, or the so-called paretic type of curve, as a rule, has a more serious prognosis than others.

Following successful antisyphilitic treatment, cell counts become normal within 3 or 4 months after treatment protein determinations which were markedly elevated prior to treatment may not be normal in some cases until 2 years after therapy very sensitive colloidal gold tests may require more than 5 years to become normal. As a rule, the last spinal fluid tests to become normal are the complement fixation reaction and colloidal gold tests, which may not be negative in some cases for more than 7 years after treatment.

Why it takes so long for abnormal protein values to become normal *following treatment of some cases of late neurosyphilis* is difficult to understand. Very high total protein determinations in patients treated for neurosyphilis of 2 or 3 years' duration usually become normal within 6 months after therapy but in cases of late neurosyphilis the total protein occasionally fails to become normal for 2 years. Presumably healing begins with the institution of effective antisyphilitic treatment, and it seems unlikely that the healing process continues for 2 years in the absence of infection. Yet, at Bellevue Hospital we have not observed a relapse in

a patient treated for neurosyphilis more than 15 months after the completion of treatment. Furthermore, re treatment of patients whose spinal-fluid findings showed a steady trend toward normal values failed to hasten the rate at which the tests became normal. It may be that minor reparative processes continue for many months after a prolonged infection in the central nervous system, or there may be some other obscure reason for the persistence of increased total protein in the spinal fluid. I do not believe that the problem can be explained by the persistence of an actual syphilitic infection in the central nervous system, or we would have seen more relapses among the patients who still had increased protein more than 1 year after treatment.

The new Lange technique for colloidal gold tests gives more consistent results than the older method but the new test is also much more sensitive than the older one, with the result that abnormal curves persist longer after treatment. Among our patients treated for neurosyphilis, the type of zone curve changed after therapy in some cases, and in others it did not. Quantitative results determined by adding the figures of all 10 tubes showed a gradual fall in all cases after successful treatment, but normal readings of 45 or less have not been obtained in some cases for more than 4 years. The reason for this is as obscure as that for the persistence of high total protein values. I do not believe that we are yet able to interpret abnormal colloidal curves with accuracy The more I studied the curves following therapy of active neurosyphilis, the more difficult it became to interpret them, but the fact remains that, following successful therapy the colloidal tests continued to show a gradual trend toward normal values, and the trend was not altered by re-treatment of patients who showed no evidence of relapse.

Our belief that the pattern of spinal-fluid tests accurately reflects the activity of a syphilitic process in the central nervous system is not based on theory but on the observation of large numbers of neurosyphilitics treated with various types of therapy including malaria, artificial hyperpyrexia, and penicillin. Dattner who was the first to recognize the full significance of the spinal-fluid pattern arrived at his conclusions after prolonged follow-up of many patients treated with malaria in Wagner Jauregg's clinic in Vienna.

Few rules in syphilis are without exceptions, and it would be a mistake to insist that normal cell counts and protein values in the spinal fluid are always proof of the inactivity of a syphilitic process in the central nervous system In our experience at Bellevue Hospital, however it has been extremely difficult to prove active neurosyphilis in the presence of normal cell counts and protein values in the spinal fluid.

FIG. 26. SPINAL-FLUID TESTS FOLLOWING TREATMENT FOR TABOPARESIS WITH TERTIAN MALARIA FOLLOWED BY 10 DAILY INJECTIONS OF 0.06 GM ARSENOXIDE, DECEMBER 5 1939 TO JANUARY 15, 1940

	Blood STS	Spinal-Fluid Examinations						
		WASS.						
DATE	WASS.	0.5 cc	0.25 cc	0.1 cc	CELLS	PANDY	TOTAL PROTEIN	COLLOIDAL GOLD
12/ 5/39	4+	4+	4+	4+	150/3	4+	150	5555555300
7 22 40	4+	4+	4+	4+	6/3	3+	65	4443210000
9 9 40	4+	4+	4+	4+	11/3	4+	60	4445555210
1 20 41	2+	4+	4+	4+	11/3	3+	55	5544321100
4 22 41	2+	4+	4+	4+	8/3	3+	45	5554443210
10 21 41	4+	4+	4+	Neg.	5/3	2+	30	0000011210
4 6 42	2+	4+	4+	Neg.	3/3	3+	39	5554443321
10 20 42	2+	4+	4+	Neg.	5/3	2+	34	0011000000
5 4 43	1+	4+	1+	Neg.	2/3	1+	30	1110000000
4 13 44	Neg.	4+	Neg.	Neg.	5/3	1+	32	0123110000
9 25 44	Neg.	4+	Neg	Neg.	3/3	Tr	33	0000000000
3 1 45	Neg.	2+	Neg.	Neg.	4/3	Neg.	34	0000000000
3 7 46	Neg.	1+	Neg.	Neg.	8/3	Neg.	33	0000000000
10 10 46	Neg.	Neg.	Neg.	Neg.	6/3	Neg.	30	0000000000
4 10 47	Neg.	Neg	Neg.	Neg	3/3	Neg.	30	0000000000

FIG. 27 SATISFACTORY RESPONSE OF SPINAL-FLUID FINDINGS IN PATIENT TREATED FOR TABOPARESIS WITH 6,000,000 UNITS OF PENICILLIN (40,000 UNITS EVERY 3 HOURS FOR 150 DOSES) JUNE 2, 1946, TO JUNE 21 1946

	Blood STS		Spinal Fluid Examinations				
DATE	M FIX. TITER	KAHN TITER	COMP FIX. TITER	CELLS	DY	TOTAL PROTEIN	COLLOIDAL GOLD
5/22, 45	570	512	330	23/3	4+	96	18,18,18,18,18,18,18,18,18,18(180)
8 21 45	310	2018	360	20/3	1+	88	18,18,18,18,18,18,18,18,17 14(175)
9 17 45	150	256	270	15/3	+	25	18,18,18,18,18,18,18,18,17 13(174)
10 15 45	150	512					
1 14 46	130	512	98	7 3	1+	46	18,18,18,18,18,18,18,17 16,9(168)
2 11 46	130	256					
3 11 46	110	128					
4 8 46	100	128					
5 8 46	Not done	128					
6 5 46	100	128	53	8/3	V F T	38	19 19 19 18,19 18,17 15,8,7.5(159)
7 3 46	Not don	128					
10 2 46	80	64					
11 5 46	Not done	128					
12 4 46	100	128					
3 19 47	67	128					
4 18 47	64	64	40	7/3	Tr	33	18,18,18,18,17 16,12,9.5,5.5 4.5(137)
5 21 47	86	64					
6 25 47	84	64					
11 8 47	43	64	29	/3	V T T	31	17 17 16,16,15,14 13 12,8,7(135)

FIG. 28. SATISFACTORY RESPONSE OF PATIENT TREATED FOR TABES DORSALIS WITH 4,000,000 UNITS OF PENICILLIN (40,000 UNITS EVERY 3 HOURS FOR 100 DOSES) OCTOBER 18, 1945, TO OCTOBER 27 1945 PATIENT HAD HAD 5 YEARS OF ROUTINE TREATMENT WITH BISMUTH AND ARSENICAL DRUGS

	Blood STS		Spinal-Fluid Examinations				
DATE	COMP FIX. TITER	KAHN TITER	COM FIX. TITER	CELLS	KEY	TOTAL PROTEIN	COLLOIDAL GOLD
10/18 44	21	3	13	370/3	2+	48	9 13,15 16,15 15 14,9,8,6(120)
10 28 44	17	3	30	232/3	1+	40	13 15 16,16,16,14 12,9.5,8,4.5(124)
12 2 44	12	3	35	220/3	T	44	9 13 14 13,14 13 12,8.5,6.5,5(110)
1 8 45	13	3					
2 3 45	7	2	12	20/3	V.F T	29	6,8,9 11,9,8,7.5,5,5,5(74)
3 3 45	4	2					
4 4 45	6	1					
5 26 45	8		11	12/3	Neg.	33	7,8 5,8.5,9,8.5,6,5,3.5,2.5,2(61)
7 21 45	4	2					
10 19 45	6	3	5	7/3	Neg	25	4.5 6.5 7.5,8,8.5,8,6,4.5,3.5,2(59)
11 17 45	6	2					
12 15 45	5	3					
2 16 46	4	3					
3 16 46	3	2					
4 20 46	7	2					
5 16 46	7	3					5,5 7.5,8,8.5,8,7.5,6.5,3.5,2.5(62)
7 20 46	3	1					
8 11 46	4	3					
9 21 46	3	2	3	7/3	±	23	5 6.5 6 5 7 7.5 6.5,4.5 4,2.5,2(52)
10 26 46	3	3					
3 8 47	6	3					
5 29 47	5	0					
6 7 47				5/3	±	20	5,5.5 6.5 7 6,6.5,3.5,2.5 1.5(49)
10 18 47	4	0	2	1/3	Neg.	20	5.5,8,8,7.5 7,6.5,5,3.5,2,1(54)

FIG. 29. SATISFACTORY RESPONSE OF SPINAL-FLUID FINDINGS IN PATIENT TREATED FOR MENINGOVASCULAR SYPHILIS WITH 4,500,000 UNITS OF PENICILLIN (30,000 UNITS EVERY 3 HOURS FOR 150 DOSES) THE REAGIN TITERS OF THE BLOOD IN THIS CASE ARE EXCEPTIONALLY HIGH. NOTE DROP IN COMPLEMENT FIXATION TITERS OF BLOOD AND ONLY FLUCTUATIONS OF KAHN TITERS. TREATED JUNE 19, 1945, TO JULY 8, 1945

Blood STS			Spinal Fl d Examinations				
DATE	M FIX. TITER	KAHN TITER	COMP FIX. TITER	CELLS	ANDY	TOTAL PROTEIN	COLLOIDAL GOLD
6/18/45	610	2048	30	45/3	2+	60	11 13 13 14 11 15 14 1..11 6(123)
7 9 45	490	2048	30	34 3	3+	77	8.5 14 15 16,17 18,17 15 7.5,7(135)
8 6 45	590	2048					
9 11 45	640	2048					
10 2 45	350	2048	7	6/3	2+	40	7,8.5 15 13 13,12,11 10,8.5,5(103)
11 26 45	400	2048					
12 28 45	510	2048	7	4 3	1+	42	6,8,9 13 15 11,8,6.5,5.5,3.5(86)
2 18 46	400	2048					
4 15 46	300	2048					
6 10 46	230	1024					
7 8 46	Not done	1024	6	7/3	±	40	5.5 6.5 8,9,9,8.5,8,6,4,3(68)
8 5 46	Not done	1024					
9 3 46	Not don	512					
10 21 46	Not done	512					
11 27 46	300	2048	5	5/3	±	39	6,8.5,8.5,8,8,7.5,5 4.5,2.5,1.5(61)
12 30 46	260	2048					
1 29 47	300	512					
2 28 47	270	1024					
3 2 47	210	2048					
6 29 47	220	1024	4	0	±	40	5,5 7.5,9,8.5,8.5,6,6.5 4(65)
7 2 47	190	512					
10 1 47	240	512					
12 27 47	240	2048	3	4/3	±	39	5,6.5 7.5,8.5,8,7.5 7.5 6.5,5.5 4(67)

FIG. 30. SATISFACTORY RESPONSE OF PATIENT TREATED FOR MENINGOVASCULAR SYPHILIS AND ANEURYSMAL DILATATION OF AORTA WITH 4,500,000 UNITS OF PENICILLIN (30,000 UNITS EVERY 3 HOURS FOR 150 DOSES) MARCH 7 1945 TO MARCH 26, 1945. PATIENT HAD HAD 2 YEARS OF REGULAR ROUTINE TREATMENT WITH BISMUTH AND ARSENICAL DRUGS

	Blood STS		Spinal-Fluid Examinations				
DATE	COM FIX. TITER	KAHN TITER	COM FIX. TITER	CELLS	PANDY	TOTAL PROTEIN	COLLOIDAL GOLD
3/ 7/45	98	4	140	540/3	4+	80	8,9.5,9.5,9.5 16,17 17 13,9 6.5(115)
3 26 45	94	32	88	34/3	1+	45	8.5 11 13 13 17 17 16,13,8.5,7.5(129)
4 28 45	70	4					
6 23 45	56	4	45	12/3	1+	38	7 7.5,8.5,10,17 16,15,8,6.5 4(100)
7 30 45	60	32					
8 25 45	56	32					
9 29 45	43	4	20	7/3	±	35	6 5 7.5,9.5 12,11 11 16,9 7,5(94)
1 15 46	49	4					
2 2 46	54	4					
4 4 46	50	4					
5 2 46	34	4	16	2/3	±	29	6,8.5,9 10,9,9 7.5 6,4,3(72)
7 8 46	39	4					
8 8 46	39	8	15	3/3	Neg.	23	7,8,9,9,8,7,5,3,3,2(63)
10 3 46	34	8					
11 7 46	42	8	15	5/3	Neg.	24	5,7,8.5,8 5,8,7.5,6,4.5,3,2(60)
1 9 47	51	16					
2 6 47	29	32					
3 7 47	30	16					
4 17 47	33	8					
7 10 47	29	8	17	2/3	Neg.	28	3.5,5,5.5,6,6.5,6,5,3,2.5,1(44)
10 2 47	32	-1					
1 10 48	32	Neg.	14	2/3	Neg.	27	4 4.5,5.5 7 6 5,6,5,3.5,2.5 1(45)

FIG. 31 RELAPSE OF PATIENT TREATED FOR ASYMPTOMATIC NEUROSYPHILIS WITH 2,000,000 UNITS OF PENICILLIN (20,000 UNITS EVERY 3 HOURS FOR 100 DOSES) DECEMBER 28, 1944 TO JANUARY 10, 1945

	Blood STS		Spinal-Fluid Examinations				
TE	COMP. FIX. TITER	K. HN TITER	COM. FIX. TITER	CELLS	NDY	TOTAL PROTEIN	COLLOIDAL GOLD
12/28/44	41	64	16	139/3	±	17	13 16,15 14,9.5,8,6,4,2.5 1.5(89)
1 10 45	48	32					
2 14 45	43	64					
3 23 45	46	64	6	9/3	Neg.	15	8.5,11 10,8.5 7.5,6.5 4,2.5 1.5(65)
4 12 45	48	3					
5 25 45	42	32					
6 11 45	45	64					
7 16 45	43	64					
8 13 45	42	64	12	44/3	±	20	10 15 14 14,9 8.5,6,6,3.5,2(88)

FIG. 31 (*Cont'd*)

PATIENT RE-TREATED WITH 6,000,000 UNITS OF PENICILLIN (40,000 UNITS EVERY 3 HOURS FOR 150 DOSES) OCTOBER 19 1945 TO NOVEMBER 7 1945

DATE	Blood STS COM FIX. TITER	KAHN TITER	COMP FIX. TITER	Spinal Fluid Examinations CELLS	ANDY	TOTAL PROTEIN	COLLOIDAL GOLD
10/19 45	37	32	11	102/3	1+	21	14 15 16,15,10,9,8,6.5,5,2(101)
11 7 45	Not done	32					
12 18 45	37	32					
1 16 46	33	32					
2 22 46	32	32					
3 21 46	31	32					
4 25 46	32	32					
6 8 46	Not done	8					
7 29 40	Not done	16					
8 26 46	Not done	16					
10 2 46	27	8					
10 30 46	29	32	5	9/3	Neg.	16	11 11 12,8.5,6,5.5,3,2,.5,.5(60)
1 20 47	Not done	16					
3 28 47	29	32					
5 6 47	21	32					
8 8 47	20	8	5	3/3	Neg.	16	9 12,11,8,6.5 4,5,3,2,1.5(62)
10 21 47	20	8					
1 29 48	18	3					

Therapeutic tests are justified when one is convinced that syphilitic activity may account for progressive clinical symptoms in the absence of signs of activity in the spinal fluid but, in our experience, therapy has seldom proved effective in such cases.

The desideratum of all treatment is the restoration of impaired function, but antisyphilitic treatment designed to destroy treponemes cannot replace scar tissue or restore function when irreparable damage to essential nerve tissue has occurred. Nor does clinical improvement of a patient following treatment of neurosyphilis prove that the syphilitic infection has been arrested Remissions and relapses are common occurrences in general paresis. At Bellevue Hospital we have observed marked clinical improvement in patients treated for neurosyphilis when the spinal-fluid findings proved that the infection had not been arrested. Consequently spinal-fluid examinations at intervals of 3 to 6 months following treatment are by far the best guide to the effectiveness of treatment of neurosyphilis.

An illustration of the response of spinal-fluid findings following malaria therapy of a patient with taboparesis is given in Fig 26 This patient has been followed up for 7 years the spinal fluid findings are reported by the older methods of determining Wassermann reactions and colloidal gold curves.

Four examples of the response of blood and spinal-fluid findings following penicillin therapy for various types of neurosyphilis are shown in Figs. 27 28 29 and 30

Figure 31 illustrates a relapse following penicillin therapy for asymptomatic neurosyphilis, and success after re treatment.

TECHNIQUES OF OBTAINING SPINAL FLUID

Spinal fluid examinations are of such great importance in the management of syphilis that the procedure for obtaining the fluid should be as simple and convenient for the patient as possible. In a large syphilis clinic the number of spinal fluids obtained depends largely on the attitude of the clinic staff and the expertness with which spinal punctures are made. In experienced hands either a lumbar tap or cisternal puncture causes very little pain, and hospitalization is unnecessary for either procedure.

In most cases patients can be persuaded to have a lumbar or cisternal puncture, provided the procedure is regarded by the clinic staff in the same matter-of fact and routine way as a blood test, and provided a physician or nurse takes the trouble to explain the reasons why spinal-fluid examinations are necessary When patients are made to understand that involvement of the brain and spinal cord can only be determined by

spinal-fluid examinations, that a negative report means reassurance for them, and that a positive report represents impending serious trouble unless proper treatment arrests the process, most will accept the tests.

LUMBAR PUNCTURE

The technique of lumbar puncture can be learned only by observing the procedure in the hands of experts. In my judgment, it is a mistake to give the impression that a spinal puncture is a procedure comparable to an operation. Beyond scrubbing his hands and pouring alcohol on his fingers, elaborate preparations by the physician are unnecessary Rubber gloves and sterile gowns need not be used. The patient can be prepared by exposing the lower back and painting the area where the puncture will be made with a good skin antiseptic which can be washed off by sterile gauze soaked in 70 per cent alcohol. The needle used for the puncture should be no larger than 20 gauge, and the puncture can be made with the patient either sitting or lying on the side with the knees drawn up. In either case it is important that the back should be arched so that the vertebrae are not drawn together If the stylet is withdrawn from the needle before entering the intrathecal space, blood is likely to enter the needle. In such a case, after the point of the needle has pierced the meninges, spinal fluid should be permitted to flow through the needle until all blood cells have been removed before the fluid is collected for testing Many a spinal-fluid specimen has been ruined for accurate testing because of red blood cells in the fluid. Every effort should be made to collect fluid which is uncontaminated by the slightest amount of blood.

After the needle has been withdrawn, the patient should be allowed to get up immediately Nothing is gained and sometimes considerable psychic damage is done by keeping the patient flat in bed, with no pillow for several hours. The purpose of keeping patients lying down after a lumbar puncture is to prevent headache. Abundant evidence has now been accumulated to prove that the recumbent position for hours after a lumbar tap increases the incidence of headaches rather than decreases it.

Davenport and Blau working in separate clinics of the New York City Department of Health, found that when patients were told to leave the clinic and engage in their usual pursuits following lumbar punctures, fewer headaches occurred than when patients were kept in the recumbent position for 10 minutes or more in the clinic and told to go home to bed. Adler working at the Elmira Reformatory at Elmira, N Y., has reported observations similar to those of Davenport and Blau. If a patient develops a postlumbar-puncture headache, the recumbent position affords the best,

Pathology of the Nervous System, ed. by W Penfield Paul B Hoeber Inc., New York, 1932

BRAIN W R. *Diseas s of the Nervous System* 2nd ed., Oxford University Press, London, 1940

DATTNER, B *The M nagement of Neurosyphilis* Grune & Stratton, Inc., New York, 1944

DAVENPORT K M "Postpuncture Reactions," *New York State J Med.*, 39 1185 1939

GREENFIELD J G and CARMICHAEL, E. A *The Cerebrospinal Fluid in Clinical Diagnosis* Macmillan & Co., Ltd., London, 1925

HARRIS AD Quantitative Serologic Tests for Syphilis. I Standard Method of Reporting" *J Ven Dis I form.* 28 219 1947

KAHN R. L. *Technique of Standard Kahn T st and of Special K hn Procedures* University of Michigan Press, Ann Arbor 1946

KOLLMER J A., and BOERNER, F *Approved Laboratory Technic* 4th ed., D Appleton-Century Company Inc., New York, 1945.

LANGE, C. "Methods for the Examination of Spinal Fluid," *Am. J Syph Gonor & V en Dis* 23 638 1939

——— Interpretation of Findings in the Cerebrospinal Fluid. I Dementia Paralytica Formula and the Necessity of Its Quantitative Differentiation *A ch Neurol & Psychiat* 53 116 1945

——— and HARRIS, A. H. "A Citrate Gold of Optimal and Reproducible Sensitivity for Use in the Colloidal Gold Reaction. Its Preparation and Control *Am J Pub Health* 34 1087 1944

——— and ——— "The Significance of the pH in the Gold Reaction, *J Lab & Clin. Med.*, 29 970, 1944

LAPORTE, R PEREZ J J and HARDRÉ DE LOOZE, L. "Sur les propriétés antigeniques de la réagine syphilitique," *Ann. Inst Pasteur* 72 678, 1946.

MAILLARD E. R. and ORZEL, A. "The Value of the Quantitatively Standardized Complement Fixation Test in the Diagnosis and Treatment of Early Syphilis," *Am. J Syph. Gono & Ven. Dis* 30 490 1946.

——— and ——— "The Value of Quantitatively Standardized Laboratory Tests in Neurosyphilis, *Am. J Syph. Gonor & Ven. Dis.*, 31 506, 1947

MERRITT H H. and FREMONT-SMITH F *The Cerebro pinal Fluid*, W B. Saunders Company Philadelphia, 1938

NEEL, A. V *The C ntent f Cells a d P oteins n the Normal Cerebrospinal Fluid The Diagnost c Importan e of Demonst at ng Small Pathological Change in the C lls and P oteins Th T chnique of the Investigation*, Munksgaard Copenhagen 1939

NEURATH H ET AL Biologic False Positive Reaction in Serologic Tests for Syphilis, *Am J Syph. Gonor & Ven Dis* 31 347 1947

REIN C. R. "The Serologic Tests in Penicillin-treated Syphilis," *New York State J M d* 47 2450 1947

——— and KENT J F False Positive Tests for Syphilis A Study of Their Incidence in Sporozoite-Induced Vivax Malaria," *J.A.M.A* 135 1001 1947

ROSENTHAL, T and SOBEL, N "Syphilis in Army Separatees," *New York State J Med* 46 2012, 1946.

SHAFFER, L. W "Nonspecific Serologic Tests for Syphilis," *Am. J Syph Gonor & Ven Dis.*, 31 221 1947

SHEPHERD M. C.: "Significance and Interpretation of Quantitative Blood Tests for Syphilis, *J Ven. Dis. Inform.*, 28 86 1947

TALMAGE, W R. DUNN C. W and GREATEALE, Z. L. Effect of Battle Casualties on Serodiagnostic Tests for Syphilis, *Bull. U.S Army M Dept.*, 6 741 1946

THOMAS E. W "The Clinical Significance of Quantitative Serologic Tests for Syphilis," *Am. J Syph. Gonor & Ven Dis.* 30 317 1946

WADSWORTH A. MALTANER, F and MALTANER, E. "Quantitative Studies of the Complement Fixation Reaction with Syphilitic Serum and Tissue Extract Technic of the Practical Quantitative Test," *J Immunol.*, 35 217 1938.

CHAPTER 5

IODIDES BISMUTH ARSENICALS, AND FEVER THERAPY

ALTHOUGH penicillin promises to supersede all previous antisyphilitic agents, bismuth, arsenoxide, and fever therapy will probably continue to have a place in the treatment of some cases of syphilis. In prepenicillin years antisyphilitic therapy demanded a thorough knowledge of the various preparations of bismuth and arsenical drugs and the reactions caused by them. The physician required expert knowledge of what to look for in the way of reactions, when to interrupt treatment because of them, and when to continue it in spite of them. All too frequently in past years the fear of reactions resulted in inadequate therapy because of the reduction in dosage of arsenical drugs. Weekly injections of 0 15 to 0.3 gm neoarsphenamine or of 0 01 to 0 03 gm arsenoxide will not necessarily prevent serious reactions in patients who are intolerant of the drugs, and such doses represent poor antisyphilitic treatment. Now that penicillin is available, concern over reactions to the arsenicals is less important, since penicillin may be used in patients who have even mild arsenical reactions. Therefore, in the sections which follow I have purposely limited discussion of the heavy metals, arsenicals, and fever therapy to the information which seems to me most essential.

MERCURY

Antisyphilitic therapy with mercury a protoplasmic poison, is practically obsolete. If mercury is used at all, the best method of administration is by inunctions.

IODIDES

Due to their effect on granulomatous tissue, the iodides may still have value in the treatment of syphilis. Iodides, so far as is known, have little effect on treponemes, but they aid in the resolution of granulomas. Jobling

and Petersen proposed the theory that the iodine radicle combines with antiproteolytic ferments in granulomatous tissue, thereby permitting autolysis by ferments formerly inhibited by antiferments. This theory may or may not be correct, but the effect of iodides on granulomas was proved at least once in the Dermatological Service at Bellevue Hospital when a skin gumma of 5 months duration healed with large doses of iodides.

Potassium iodide is used in a saturated solution and is given only by mouth. The usual dose is 2 to 3 gm, three times daily There is no virtue in the practice of starting potassium iodide in low doses and gradually increasing the dose.

Sodium iodide can be given intramuscularly or intravenously It is usually prepared in a 10 or 20 per cent solution and is given in doses of 2 to 10 gm, three or four times weekly Sodium iodide is excreted rapidly

The iodides are believed to have value in the treatment of gummas, cardiovascular syphilis, and neurosyphilis.

Toxic effects.—Serious reactions to iodides are rare, but potassium iodide frequently causes gastrointestinal irritation and an annoying metallic taste in the mouth. Catarrh of the mucous membranes and skin eruptions may be produced by either potassium or sodium iodide. A few instances of death due to gangrenous, ulcerative iodide eruptions have been recorded.

Contraindications.—The chief contraindications to the use of iodides in syphilis are concurrent tuberculosis or thyroid disease.

BISMUTH

Bismuth, first introduced by Sazerac and Levaditi in 1921 is a less effective treponemicidal agent than the arsenicals.

Preparations.—Three types of bismuth preparations are available for intramuscular injections (1) water-soluble preparations, (2) oil-soluble preparations, and (3) suspensions of insoluble bismuth subsalicylate in oil.

If rapid absorption and elimination of bismuth are desired, water soluble preparations are given intramuscularly three to five times weekly Oil-soluble preparations are absorbed more slowly than aqueous solutions and are eliminated less rapidly They are given by intramuscular injection at three to five-day intervals.

Insoluble bismuth in oil, the preparation of choice in most cases, usually consists of 10 per cent bismuth subsalicylate suspended in oil. Bismuth subsalicylate contains about 65 per cent metallic bismuth and the usual dose is 2 cc of the oil mixture which contains about 0.135 gm metallic bismuth.

The absorption and elimination of bismuth subsalicylate in oil are slow According to Cole, a continuous daily urinary excretion of 2 to 4 mgm bismuth indicates the presence of therapeutic tissue concentrations, and weekly injections of from 1 to 2 cc bismuth subsalicylate in oil will yield a continuous excretion of at least this amount of bismuth. Few situations occur where insoluble salts of bismuth in oil will not serve the same purpose as soluble preparations which must be given more frequently

In recent years we have learned that bismuth subsalicylate in oil can be given every other day for at least 10 days with relative safety With such intensive treatment, deposits of the drug undoubtedly remain in the muscle for several months and during much of this time, probably provide sufficient bismuth to protect against relapse and reinfection. This is not always true, as several patients treated for early syphilis returned to Bellevue Hospital with dark field positive lesions within 4 months after treatment courses that included four or five injections of 0.2 gm bismuth subsalicylate in oil within an 8-day period.

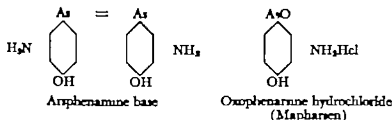
Oral administration of bismuth.—Bismuth is absorbed from the gastrointestinal tract and can be given in daily doses of 0.5 gm to 1 gm metallic bismuth. Sodium bismuthate, called Sobisminol, in doses of 2 capsules three times daily heals skin gummas and probably has much the same effect as bismuth injected intramuscularly When oral bismuth was used at Bellevue Hospital, patients frequently complained of gastrointestinal symptoms. Oral administration of bismuth is not advised, as there is no assurance that the drug will be taken as directed.

Toxic effects.—Bismuth causes remarkably few serious reactions. Rarely local tissue reactions may be so severe that further injections are inadvisable. Bismuth stomatitis can be very severe, but, fortunately it has a low incidence, even in patients with poor oral hygiene. Bismuth pigmentation of the gums and oral mucosa of patients receiving the drug is frequently seen and is harmless. Skin eruptions caused by bismuth have been described but are extremely rare. Bismuth is mildly toxic to the kidneys and should be used with caution in patients who have nephritis or nephrosis. Accidental injection into a vein causes pulmonary embolism, and into an artery necrosis and gangrene of the gluteal muscles.

TRIVALENT ARSENICAL DRUGS

As a result of Ehrlich's discovery of salvarsan (606) numerous other arsenical drugs were synthesized and used to treat syphilis. The older trivalent arsphenamines, of which old arsphenamine, neoarsphenamine,

and silver arsphenamine are best known, were all derived from an arsphenamine base which has two benzene rings in its structural formula. In 1934 Tatum and Cooper reintroduced arsenoxide which had been discarded by Ehrlich and Hata. It was first marketed under the trade name of Mapharsen. Mapharsen is meta-amino-parahydroxyphenylarsine oxide (oxophenarsine hydrochloride) Later other arsenoxides (Chlorarsen and Phenylarsine hydrochloride) were placed on the market. In solution all of these products are essentially identical.



Arsphenamine base   Oxophenarsine hydrochloride (Mapharsen)

Ehrlich discarded arsenoxide because he thought it was too toxic. Today arsenoxide is emphatically the arsenical of choice, because in effective doses it is much less toxic than the other arsphenamines. The incidence of major and minor reactions has been greatly lowered by substituting arsenoxide for the older arsenicals. I have not used any of the older trivalent arsenicals since 1939 and have had no occasion to use them, but in rare instances neoarsphenamine may be tolerated better than arsenoxide, and also it may be more effective in exceptional cases.

Arsenoxide is excreted more rapidly than other trivalent arsenicals and can, therefore, be given more intensively in effective therapeutic doses. In the treatment of early syphilis from 20 to 30 mgm per kilogram of body weight are needed for the best results. Eagle found in experimental syphilis in rabbits that it made no difference therapeutically whether the required amount of Mapharsen was given in 5 days or 8 weeks. He, therefore, recommended treating early syphilis with three injections of 0 06 gm arsenoxide weekly for 8 weeks. While this schedule of treatment proved less hazardous than concentrating similar total amounts of arsenoxide in a 10-day period, it was less practical because patients frequently failed to report regularly for treatment. There is no question, however that the hazard of arsenoxide therapy is increased when more than 0 18 gm is given in divided doses during 1 week. At Bellevue Hospital, even when arsenoxide therapy was limited to three injections of 0.06 gm a week, at least 5 per cent of patients had severe gastrointestinal complaints, and occasionally more serious reactions. In a

series of 125 patients treated with three injections of 0 06 gm arsenoxide a week, 1 patient had arsenical encephalopathy If penicillin were not available the intensive use of arsenoxide would be justifiable, but there is *no longer any reason for exposing patients to the risk of serious reactions.* Nevertheless, if arsenoxide is used at all, it should be given in doses of at least 0 04 gm to 0 06 gm every 3 or 4 days. With such treatment the incidence of reactions is not appreciably greater than when injections are given at weekly intervals. On the other hand the therapeutic results are superior if only because experience has shown that patients are more likely to complete a short treatment schedule than a prolonged one.

Preparation and administration of arsenoxide.—Unlike solutions of old" arsphenamine and neoarsphenamine, arsenoxide can be dissolved in water readily and without fear of increasing its toxicity by aeration. Bubbling air through solutions of arsenoxide makes the preparation less *toxic but also, if aerated too much, less effective therapeutically* The dose of 0 06 gm arsenoxide is dissolved in 5 to 10 cc sterile double-distilled water and injected rapidly into a vein As a rule, the more rapidly the injection is made, the less likely the patient is to have pain along the vein. Nitritoid reactions, in my experience, have not been produced by rapid injection of arsenoxide solutions.

Accidental paravenous injection of arsenoxide, or any other arsenical, should be scrupulously guarded against, since it results in severe pain and, at times, sterile abscess and sloughing of tissue. Even a few drops of solution outside of the vein will cause pain.

REACTIONS TO ARSENOXIDE THERAPY

The Jarisch-Herxheimer reaction (therapeutic shock) will be discussed in the section on reactions to penicillin therapy of syphilis. Other reactions to arsenoxide therapy are described in this section in the order of their frequency

Gastrointestinal reactions.—Nausea and vomiting are frequently associated with arsenoxide therapy When moderate, these complaints are not contraindications to continuing the injections. Occasionally however nausea and vomiting are so severe and prolonged that further injections are impossible. In mild reactions nausea can frequently be prevented by having the patient eat chocolate or some other sweet during the injection. Anxiety and fear of the injections increase the tendency to gastrointestinal complaints.

Acute arsenical erythema (ninth-day erythema of Milian) —All trivalent arsenical drugs including arsenoxide may cause an acute reaction

which begins on the sixth to the twelfth day following the first injection of the drug, regardless of how frequently injections are given. Milian, who first described the reaction in 1917 believed it was due to the activation of a latent infection such as measles or scarlet fever (biotropism) Although there is no evidence to confirm this opinion, the reaction does resemble an acute infection. Its first sign is usually fever and occasionally the only evidences of the reaction are an elevated temperature and malaise. In most cases, however the rise in temperature is followed within 24 hours by a generalized morbilliform or scarlatiniform eruption which may or may not be associated with lymphadenitis and pharyngitis. Rarely in patients receiving arsenotherapy acute arsenical erythemas have been associated with arsenical encephalopathy The presence of excessive amounts of protein in the spinal fluid of such patients confirms the diagnosis of encephalopathy

Acute arsenical erythemas rarely last more than 4 or 5 days, and the subjective complaints are usually mild. The occurrence of the reaction necessitates interrupting arsenical therapy for at least 3 to 4 weeks, after which time the patient usually tolerates continued treatment with arsenicals. Occasionally however recurrent attacks of fever and erythema and other more serious reactions such as hepatitis, agranulocytosis, and nephritis have occurred when arsenical therapy was resumed. Leifer in 1945 reported that in 14 patients early continuation of arsenic after the initial reaction led to serious damage, in the form of jaundice and agranulocytosis, with or without nephritis. In every instance where resumption of treatment with arsenical drugs is necessary and penicillin cannot be used, it should be started very cautiously and with small doses.

Arsenical encephalopathy —When arsenoxide is given in daily injections of 0.1 gm or more, the next most frequent reaction is encephalopathy The incidence of this serious reaction is extremely low when injections totaling not more than 0 12 gm arsenoxide are given weekly At Bellevue Hospital 0.3 per cent of the patients treated for early syphilis with as much as 1.2 gm arsenoxide in a 7 to 10-day period died as a result of encephalopathy

This reaction may occur at any time after the onset of arsenical treatment. Cases of encephalopathy have been described following as little as two injections of 0.3 gm neoarsphenamine, but such reactions to small doses occur so rarely as to be almost negligible. The reaction may begin abruptly with convulsions, or there may be premonitory signs of fever headache, twitchings, spots before the eyes, nervousness, and anxiety The diagnosis can always be made by examining the spinal fluid, as the total

protein is markedly increased in all cases of arsenical encephalopathy Values of over 400 mgm per cent were found in two patients with fatal reactions observed at Bellevue Hospital All but 1 of the 20 patients with arsenical encephalopathy observed at Bellevue Hospital recovered or died within 4 to 7 days after the onset of symptoms the one exception became progressively worse for 2 weeks before fatal termination. Complete recovery occurred in 16 of the 20 patients.

The reports of pathological changes noted in the brains of individuals who died with arsenical encephalopathy have varied from marked cellular infiltration with or without perivascular hemorrhages to no notable pathology Apparently the reaction is vascular and allergic. Evidence of marked edema of the brain has not been noteworthy at autopsy but in all probability some edema of the brain occurs during the reaction.

Numerous suggestions for the treatment of arsenical encephalopathy have been made, but, in our experience at Bellevue Hospital, the treatment of choice is sedation Sufficiently large doses of sedatives must be given to control the convulsions and keep the patient at rest. Morphine is valuable. We used sodium amytal or sodium phenobarbital intravenously or intramuscularly to control convulsions. During serious reactions thorough neurologic examinations should be discouraged they serve no good purpose and disturb the patient. Injections of 0.8 to 1 cc of 1 1000 solution of epinephrin have been suggested for the treatment of arsenical encephalopathy they were tried at Bellevue Hospital with poor results. Dehydration with 50 cc of 50 per cent sucrose intravenously can be tried and may be of some value, but infusions of 5 per cent glucose may have to be given subsequently to patients who are unable to take fluids by mouth. BAL (2 3 dimercaptopropanol) should be given in doses of *2 5 mgm per kilogram of body weight every 4 hours for the first 2 days* and once or twice a day for 5 or 6 days, even though its value in arsenical encephalopathy is doubtful. Prebble, who has reported by far the largest number of arsenical encephalopathies, does not recommend BAL. That BAL is an effective antiarsenical has been demonstrated in numerous cases, but my experience in using it in only a few cases of encephalopathy led to no definite conclusions.

Arsenical hepatitis.—The reported incidence of jaundice caused by arsenical hepatitis varies greatly At Bellevue Hospital jaundice occurred in about 0.3 per cent of patients given massive arsenotherapy with arsenoxide. Organic arsenic is known to produce liver necrosis in animals, and arsenicals should be avoided in the presence of liver damage. The discrepancies in the reported incidence of jaundice during arsenical therapy

may be due to the fact that associated liver disease or infections accounted for some of the reported cases. Arsenical hepatitis rarely results in any serious sequelae, but fatal cases of acute yellow atrophy have occurred. Jaundice occurring in patients several months after the last injection of arsenical drugs has been attributed to the delayed action of arsenic, but proof that the hepatitis in such cases was due to arsenical treatment is lacking.

Blood dyscrasias.—Agranulocytosis and aplastic anemias may be caused by any of the arsenicals. Such reactions are very rare in my experience, but Holley has recently reported 12 cases of agranulocytosis occurring during massive arsenotherapy of early syphilis. All were treated with BAL, and all recovered. The dosage of BAL was the same as that described in the section on arsenical encephalopathy In patients who have had blood dyscrasias due to arsenotherapy further injections of arsenical drugs should be prohibited.

Arsenical dermatitides.—When the older arsphenamines were used, skin eruptions were one of the major reactions to treatment. The incidence of such reactions was greatly lowered when arsenoxide was substituted for "old arsphenamine and neoarsphenamine. Exfoliative dermatitis, the most serious and disabling of the skin reactions to organic arsenic, is very rare with arsenoxide therapy Urticaria and patchy eczematoid dermatitis have been associated with arsenoxide therapy in a few cases at Bellevue Hospital.

Nitritoid reactions.—In treatment with old" arsphenamine and neoarsphenamine, nitritoid reactions during the injection or soon thereafter were not unusual. In such reactions the patient complains of feeling hot, becomes flushed, perspires, and may lose consciousness the pulse is almost imperceptible, and the blood pressure is unobtainable. Subcutaneous injections of 5 to 8 minims of 1 1000 solution of epinephrin are usually followed by prompt recovery In susceptible individuals the reaction can be prevented in most cases by small doses of epinephrin before the arsenical is injected. Nitritoid reactions have practically been eliminated by substituting arsenoxide for the older arsphenamines.

PENTAVALENT ARSENICALS

The best known pentavalent arsenicals are Tryparsamide and Acetarsone (Stovarsol) Neither drug is as treponemicidal as are the trivalent arsenicals, although Acetarsone, either by oral administration in the form of tablets or by intravenous injection, will cause more rapid healing of early

syphilitic lesions than Tryparsamide. Stovarsol, in the form of tablets administered orally has been used in the treatment of congenital syphilis because of ease of administration but it has not proved as effective as the trivalent arsenicals.

For the most part, pentavalent arsenicals have been used for the treatment of neurosyphilis. The drug most commonly chosen in America has been Tryparsamide, which is the least treponemicidal of all the organic arsenic preparations used in syphilis. For unknown reasons, the pentavalent arsenicals have proved more effective in the chemotherapy of general paresis, and perhaps other forms of neurosyphilis, than the trivalent arsenicals. But, in spite of this fact, Tryparsamide is so inferior to fever therapy and penicillin in the treatment of neurosyphilis that it deserves little consideration today The incidence of optic nerve injury due to Tryparsamide is sufficiently high to make its use hazardous, and the therapeutic results, in my opinion do not warrant its continued use. In 1938, I reviewed the charts of 250 patients who had received large amounts of Tryparsamide at Bellevue Hospital. Except in cases of general paresis where it appeared to prolong life, I could come to no definite conclusions as to its value in neurosyphilis. In 1939 following severe injury to the optic nerves of two patients at Bellevue Hospital, we abandoned the use of Tryparsamide entirely

FEVER THERAPY

The beneficial effects of fever in the treatment of syphilis were first discovered by *Wagner Jauregg whose interest was aroused by his* clinical observations that patients with psychoses occasionally improved after fevers. Following this observation, almost 30 years passed before Wagner Jauregg discovered that general paresis could be checked by fever and that induced malaria was the most efficient febrile agent.

The search for an explanation of the beneficial results of malaria in general paresis led to much speculation and controversy but to very little scientific investigation of fever per se for almost two decades. In some quarters the controversy still continues over the relative value of malaria and artificial hyperpyrexia in the treatment of neurosyphilis. In spite of differences of opinion, the available evidence indicates that fever regardless of how it is produced, is a valuable antisyphilitic agent. Boak, *Carpenter and Warren have demonstrated in rabbits that* T pallidum is killed in vivo by temperatures of 42 C maintained from 1 to 6 hours. In human beings, however available evidence indicates that T pallida

are not completely destroyed by temperatures which are tolerated by man. Nevertheless, the treponemes are unquestionably injured by elevating temperatures to levels of from 102 F to 105 F for 3 to 6 hours. This fact suggests that fever is a valuable adjuvant to other antisyphilitic agents. By the induction of fever with intravenous injections of typhoid vaccine at Bellevue Hospital, we were able to reduce by half the total dosage of arsenoxide necessary for the cure of early syphilis in a 10-day period. We also found that malaria therapy of all types of neurosyphilis was successful in checking the activity of the infection in 85 per cent of cases when followed by only 10 daily injections of 0 06 gm arsenoxide.

In any type of syphilis which proves resistant to other forms of antisyphilitic treatment, fever is valuable as an adjuvant to other treatment. Cases of early or late syphilis which prove resistant to arsenical drugs and penicillin should receive fever therapy Malaria or electropyrexia is preferred for neurosyphilis. From 8 to 10 fevers are usually sufficient for all forms of neurosyphilis, including general paresis. In other types of syphilis, fevers can be produced by intravenous injections of typhoid vaccine. The vaccine used at Bellevue Hospital contained 1 000 000 000 B typhosus, 750,000 000 B paratyphosus A, and 750,000,000 B paratyphosus B per cubic centimeter The first fever was induced with an initial dose of 0 1 cc of this vaccine injected intravenously the second with 0.2 cc, the third with 0 4 cc, the fourth with 0 6 cc, and the fifth with 1 cc. From 2 to 3 hours after the initial injection, if desired, another dose of equal amount can be given to prolong the fevers. The intravenous injection of typhoid vaccine causes considerable discomfort which can usually be relieved by Demerol or if necessary by morphine. In most cases it is difficult to induce more than five satisfactory fevers by intravenous injections of typhoid vaccine when fevers are induced every second or third day Better fevers are obtained when patients are well covered with three or four woolen blankets.

Hazards of fever therapy —Fever therapy is dangerous in debilitated patients and should be given with caution in all cases. The reported mortality rates attributed to malaria therapy have ranged from 5 to 20 per cent. The induction of fever with intravenous injections of typhoid vaccine is a relatively safe procedure, but at Bellevue Hospital we encountered occasional severe reactions with lowered blood pressure and feeble pulse. Now that penicillin is available, the induction of fever should be avoided unless penicillin has proved ineffective or has failed to check the syphilitic infection.

REFERENCES

BEERMAN H Fatalities Due to Bismuth in the Treatment of Syphilis, *Arch. Dermat & Syph* 26 797 1932.

BOAK R. A. CARPENTER, C M and WARREN S. L. "Concurrent Treatment with Fever and Neoarsphenamine of Experimental Syphilis in Rabbits," *Am. J Syph. Gonor & Ven. Dis.*, 26 282, 1942.

——— ——— and ——— Inadequacy of a Single Prolonged Fever for Treatment of Early Acute Syphilis," *Am. J Syph. Gonor & Ven. Dis.*, 26 291 1942.

CHARGIN L. "Toxicological Manifestations of Massive Arsenotherapy in Early Syphilis by the Continuous Intravenous Drip Method," *Arch. Dermat & Syph.* 42 247 1940

COLE, H N FARMER, H. L. and MISKJIAN H. "Intramuscular Absorption of Some Insoluble Bismuth Compounds as Revealed by the Roentgen Ray" *Arch. Dermat & Syph.*, 13 219 1926.

——— SOLLMAN T and HENDERSON K. "The Choice of a Bismuth Preparation Clinical Résumé of Excretion and Retention Studies, *Am J Syph Gonor & Ven. Dis.* 23 143 1939

EAGLE, H "On the Spirocheticidal Action of the Arsphenamines on Spirocheta Pallida in Vitro" *J Pharmacol. & Exper Therap* 64 164 1938.

——— "The Minimal Effective Concentrations of Arsenic and Bismuth Compounds on T Pallidum in Vitro in Relation to the Therapeutic Dose *Am. J Syph., Gonor & Ven. Dis* 23 310 1939

——— and MAGNUSON H J "The Systemic Treatment of Two Hundred and Twenty-seven Cases of Arsenic Poisoning (Encephalitis, Dermatitis, Blood Dyscrasias, Jaundice, Fever) with 2, 3-Dimercaptopropanol (BAL) *Am. J Syph Gonor & Ven Dis* 30 420 1946.

HOLLEY H. L. "The Use of BAL in the Treatment of Agranulocytosis Following Intensive Arsenotherapy for Syphilis," *Ann. Int Med.*, 31 231 1947

JOBLING, J W and PETERSEN W "The Therapeutic Action of Iodin, *Arch Int Med* 15 286 1915

LEIFER, W Danger of Continued Arsenotherapy in Cases of Erythema of Ninth Day *Am. J M S* 210 458, 1945

PEARCE, L "Therapeutic Action of Potassium Iodid in Experimental Syphilis of the Rabbit," *Arch. Dermat & Syph.* 12 1 1925

PREBBLE, E. E. Arsenical Encephalopathy A Review of the Literature with a Report of a Further One Hundred and Eighty-seven Cases, *Brit J Ven Dis* 22 93 and 139 1946.

Symposium on Clinical Uses of 2 3-Dimercaptopropanol (BAL) *J Clin. Investigation* 25 451 1946.

TATUM A L and COOPER, G A. "An Experimental Study of Mapharsen (Meta amino Para hydroxy Phenyl Arsine Oxide) as an Antisyphilitic Agent, *J Pharmacol. & Exper Therap* 50 198, 1934

THOMAS E. W WEXLER, G and DATTNER, B. "Cerebral Reactions Associated with Massive Mapharsen Treatment of Early Syphilis, *Am. J Syph G o & V n. Dis.*, 26 529 1942.

CHAPTER 6

ANTIBIOTICS IN THE TREATMENT OF SYPHILIS

PENICILLIN

THE observation by Fleming that the mold *Penicillium notatum* has antibacterial properties led to the discovery of penicillin, which became available for extensive clinical trial in 1942. The early investigations with this antibiotic were limited largely to combating pyogenic infections. Because he was unable to obtain penicillin, and he wanted to test its effectiveness in syphilis, Mahoney grew the mold and manufactured the antibiotic in the research laboratory of the United States Public Health Service at the Marine Hospital, Staten Island, N Y By the early months of 1943 he had learned that penicillin was an unusually potent antisyphilitic agent. His pioneer treatment of early syphilis with intramuscular injections of aqueous solutions of penicillin is now history it provided an effective plan of therapy that served as a basis for subsequent investigations.

Chemistry of penicillin.—Monographs on the chemistry of penicillin were published by the American Committee on Medical Research and the British Medical Research Council in 1945 and 1946. In 1947 a review of the chemistry of penicillin was published in *Science* Additional information on the chemistry of the various penicillins will undoubtedly be available by the time this book is published. Suffice it to say here that many different salts of penicillin have been prepared without impairing its antibiotic effect.

Salts of amorphous (noncrystalline) penicillin are unstable and are adversely affected by moisture, exposure to air and heat. The early commercial preparations were chiefly sodium, potassium, or calcium salts of amorphous penicillin. All penicillin salts are inactivated by primary alcohols, by an enzyme produced by Bacillus coli (penicillinase) and by various heavy metals. Eagle has shown that, in relatively high concentrations, arsenoxide is capable of inactivating penicillin and, therefore, penicillin should not be given in solutions containing either arsenical drugs or bismuth.

Crystalline penicillins.—Four different penicillins (G F X, and K) have been identified and crystallized in almost pure form. In the amorphous penicillin originally manufactured, G and F predominated. With changes in the mold utilized and the methods of growing the mold, in 1944 and 1945 the penicillins produced contained large amounts of K. This was unfortunate, since it was subsequently determined that penicillin K was less effective than the other known penicillins. A co-operative investigation of the therapeutic efficacy of the available crystalline penicillins in experimental syphilis in rabbits, which was sponsored by the Subcommittee on Venereal Disease of the National Research Council, proved that G was more potent (in syphilis) than F K, and X. Similar investigations by others, notably Turner Cumberland, and Huan Ying Li, confirmed this conclusion and there is general agreement today that G is the penicillin of choice. Most commercial penicillin manufactured since 1946 has been crystalline G and even amorphous penicillins now have a G content of at least 85 per cent.

Unlike amorphous penicillin crystalline G is relatively stable and need not be kept refrigerated. Its potency is preserved for long periods at ordinary temperatures, if not in aqueous solution.

Dosage of penicillin in terms of units.—Pure crystalline penicillin G can be prepared but the cost of producing it in absolutely pure form is so great that the commercial products so far have contained from 5 to 10 per cent impurities. Consequently penicillin G is still marketed in terms of units rather than of milligrams. The number of units is determined by bio-assay The variations in potency of different lots of penicillin G have been less than with different lots of amorphous penicillin, but no method of bio-assay is as exact as determining dosage by weight in milligrams. For clinical use, however such variations as exist between different lots of penicillin G probably have little practical significance. Under the present law 1 mgm of crystalline penicillin G must have a potency of about 1 666 units.

Identification of penicillin in body fluids.—The only means of identifying penicillin in blood, urine, or other body fluids is by bio-assay Various organisms can be used to test the antibacterial effect of penicillin, Sarcina lutea or B. subtilis being most commonly used. Unfortunately T pallidum cannot be used for bio-assay of penicillin. With present methods of assay (Sarcina lutea cup plate) amounts of penicillin as low as 0.01 unit per cubic centimeter can be identified in body fluids. The chief value of blood-level determinations is to ascertain the rate of absorption rather than the therapeutic efficacy of any given dosage. From

our present knowledge, in so far as syphilis is concerned, the term therapeutic blood level of penicillin has little import, since cases have been cured with relatively small amounts of the antibiotic, and others have failed with very large amounts. And, unfortunately we are unable to determine the susceptibility of the individual treponeme in vitro as we can with streptococci, staphylococci, and other organisms.

Absorption and excretion of aqueous or saline solutions of penicillin.—After intramuscular injection of penicillin in aqueous or saline solution, average doses of penicillin are rapidly absorbed and excreted, usually in 2 or 3 hours. With very large doses (over 800 000 units) demonstrable amounts of penicillin may be found in the blood for 6 to 10 hours (McDermott and Nelson)

Following intravenous and intramuscular injections of aqueous solutions, the concentration of penicillin in the blood attains a peak in 15 to 30 minutes, and this is followed by a rapid fall. Most of the injected penicillin is excreted in the urine. If continuous blood levels of penicillin are to be maintained with injections of aqueous or saline solutions, 20,000 to 50 000 units must be given intramuscularly every 2 or 3 hours the use of continuous intravenous or intramuscular drip is impractical and unnecessary

Methods of delaying the excretion or absorption of penicillin.—Various methods of delaying excretion and absorption have been used. Delayed excretion has been attained with caronamide, diodrast, and para-aminohippuric acid, but the use of drugs to block filtration of penicillin through the kidneys is less desirable and effective than delaying absorption from muscle depots. Consequently most efforts to improve penicillin preparations have been devoted to finding practical ways of delaying absorption. Each year has brought advances in the commercial products of slowly absorbed penicillin, and possibly by the time this book is published still further improvements will have been made. Up to the present, delayed absorption of penicillin has been best achieved in four ways (1) by mixing penicillin in oil and beeswax (2) by using penicillin particles of at least 50 microns in size (3) by using insoluble salts of penicillin which are slowly absorbed when mixed in oil or water and (4) by suspending small particle size procaine penicillin G in oil gelled with 2 per cent aluminum monostearate.

Penicillin in oil and beeswax.—Romansky and Rittman first devised a practical method of delaying the absorption of penicillin by mixing it with oil and 4.8 per cent beeswax. The original mixtures of this product were solid at room temperature and had to be heated to make them fluid.

REACTIONS TO PENICILLIN

While no other effective antisyphilitic agent has proved so free from serious reactions as penicillin its use has been attended with some toxic effects. Herxheimer reactions were encountered even more frequently than with arsenical drugs. Consequently before describing the reactions peculiar to penicillin, it seems advisable to consider the Jarisch Herxheimer reaction, which has been a familiar phenomenon in the treatment of syphilis since the introduction of trivalent arsenicals by Ehrlich.

The Jarisch-Herxheimer reaction (therapeutic shock) —The Jarisch-Herxheimer reaction, more frequently known as the Herxheimer reaction, is not unique to penicillin therapy of syphilis. In the treatment of early syphilis the reaction begins within 12 hours after the first injection of a potent treponemicidal agent. It consists of fever with or without exacerbations of the early syphilitic lesions, and it rarely lasts more than 24 hours. Fear of the reaction has caused some unnecessary overcaution in the treatment of secondary syphilis, e.g beginning therapy with bismuth or very small doses of arsenicals or penicillin In the treatment of thousands of cases of early syphilis at Bellevue Hospital I have never known a Herxheimer reaction to do harm. Following the initiation of therapy of early syphilis with either a trivalent arsenical or penicillin, many patients have had temperatures of 104 F or over for several hours without being aware of the fever Others complained of feeling warm or of having chills, and in the ambulatory treatment of early syphilis, large numbers of patients have undoubtedly had Herxheimer reactions without interrupting their usual way of life. Over 50 per cent of patients given penicillin for early syphilis have had fevers lasting from 2 to 8 hours.

In late syphilis Herxheimer reactions have been the subject of many conflicting and confusing reports. The incidence of such reactions in late syphilis is relatively low in my experience, but some observers have reported them in about 50 per cent of previously untreated patients. I do not know the reason for the difference between our experience at Bellevue Hospital and that of others unless we have failed to note very low and transient fevers. Fever over 100 F and demonstrable exacerbations of late syphilitic lesions, following the inception of penicillin therapy have been observed in about 10 per cent of late cases treated at Bellevue Hospital. The most notable reactions occurred in patients given penicillin for neurosyphilis. A number of these patients became psychotic, or markedly agitated, within 24 hours after penicillin therapy was started. We have observed no harmful sequelae to these reactions, in spite of the fact that

restraints were needed to control several patients. However Stokes, O'Leary Solomon, Rose, and others have reported occasional alarming reactions in patients treated for neurosyphilis with penicillin. Moore states that "several observers (ourselves, O Leary Solomon, and Rose) have seen rapid paretic deterioration develop within the first few days of treatment in patients who seemed good risks before, progressing to unexplained death within a few weeks." * Similar observations have occasionally been reported after the onset of malaria therapy Whether or not these untoward effects could have been prevented by preliminary courses of bismuth is problematical, especially since bismuth has not been effective in the treatment of general paresis.

In very rare instances Herxheimer reactions in cardiovascular syphilis have probably been the cause of serious damage and even death. In my opinion, however the menace of therapeutic shock has been exaggerated. Sudden attacks of paroxysmal dyspnea, anginal pain, or heart failure have occured in patients with syphilitic heart disease who were not being treated specifically Yet, if similar symptoms occurred within 24 hours after antisyphilitic treatment was started, they were usually attributed to a Herxheimer reaction. A pertinent incident recently occurred at Bellevue Hospital, when a patient with cardiovascular syphilis, who was waiting in line for his first injection of penicillin, suddenly collapsed and died. Although no autopsy was obtained, it is probable that he had a coronary occlusion. However if the accident had occurred a few hours after the first injection of penicillin instead of before it, the suspicion of Herxheimer reaction would have had to be entertained.

We have had no reason to believe that Herxheimer reactions caused harm to any of the patients given penicillin for cardiovascular syphilis in our service at Bellevue Hospital. On the other hand, one patient with cirrhosis of the liver might have had a harmful Herxheimer reaction This patient was referred to us from a medical ward because of untreated syphilis and cirrhosis of the liver Whether or not syphilis was the cause of the liver disease could not be determined. Treatment was started with intramuscular injections of 40,000 units of penicillin G in aqueous solution at 3-hour intervals. He had no complaints and no fever on the first day of treatment. On the third day of penicillin therapy he was found to have ascites, which was not present before treatment was started. Penicillin injections were stopped, and the patient was transferred to the medical ward where he later died from hemorrhage following rupture of

* Moore, J. E. *Penicillin in Syphilis*, Charles C. Thomas, Publishers, Springfield, Ill., 1946, p. 58.

esophageal varices. Possibly the sudden development of severe portal obstruction in this patient was due to a Herxheimer reaction.

No doubt it is a wise and safe rule to precede penicillin therapy of patients with cardiovascular syphilis and liver disease with a course of bismuth. It is quite illogical, however to give a course of bismuth before beginning penicillin therapy of late syphilis to a patient who has recently received penicillin for some other disease. Large numbers of patients with late syphilis have undoubtedly been given penicillin for some other infection, without apparent harm—a fact which has not been given enough consideration by those most concerned about Herxheimer reactions.

Not infrequently one hears of "delayed Herxheimer reactions, which occurred from a few days to several weeks after the first injection of an arsenical or penicillin. Proof that the signs and symptoms noted were due to delayed Herxheimer reactions has been lacking So far as I know there is no evidence that delayed Herxheimer reactions do occur But it must be admitted that, until we understand the mechanism of the reaction better we cannot categorically deny the possibility of delayed reactions.

In former years it was generally assumed that Herxheimer reactions were due to the rapid destruction of treponemes. This explanation still seems to me to be the moste plausible one yet there are arguments against it. Olansky has reported "severe Herxheimer reactions" in six patients with late syphilis following only 1 000 units of penicillin. Tucker and Farmer reported febrile reactions in five patients with late syphilis following the first injection of penicillin one of them received an initial dose of only 500 units, and the incidence of febrile reactions among patients started on treatment with 500 to 3 000 units of penicillin was as great as when initial doses of 25 000 to 100 000 units were used. Thus, it is difficult to believe that the reactions described were caused only by the rapid killing of large numbers of treponemes. But, in spite of this difficulty similar reactions have not been reported following penicillin treatment of other diseases. Therefore, we must assume that even small amounts of penicillin have sufficient effect on the syphilitic virus to produce the reaction. Why the reaction is observed in only about 60 per cent of patients treated for early syphilis is unknown, and we are totally ignorant of the biologic changes causing the phenomenon.

The reports of reactions following low doses of penicillin have proved the futility of trying to prevent therapeutic shock by beginning antisyphilitic treatment with very small doses of penicillin. It is conceivable, although there is no evidence on this point, that the use of small doses of penicillin might help produce penicillin-resistant strains of treponemes.

Therapeutic paradox.—The term therapeutic paradox has been used to describe anatomic damage supposedly caused by the rapid healing of late syphilitic lesions and the rapid formation of scar tissue. Reliable reports of therapeutic paradox in the treatment of syphilis are rare, but there can be no doubt that such paradoxical reactions to therapy have occurred. In cardiovascular syphilis, rapid healing might lead to distortion of the aortic valves and so cause aortic regurgitation or aggravate an already existing aortic insufficiency. It is also conceivable that rapid healing with scar formation in syphilis of the liver might be the cause of portal obstruction and ascites. Therefore, it is probably safer to begin treatment of cardiovascular syphilis and late syphilis of the liver with bismuth. How many injections of bismuth should be given before starting penicillin in these conditions, to prevent therapeutic shock or therapeutic paradox, has not been accurately determined. I believe that 3 injections of bismuth subsalicylate in oil at 5-day intervals should be sufficient preparation, but I might give more bismuth in cases where the signs and symptoms suggest a rapidly progressive active inflammation. In my opinion, it is impractical to start treatment of all late syphilis with bismuth instead of penicillin. When to begin therapy with bismuth and how much bismuth to give must depend on the individual case and the judgment of the physician responsible for therapy.

SPECIFIC REACTIONS TO PENICILLIN

The toxic reactions to penicillin have been the cause of discomfort to a small percentage of treated patients, but no serious consequences have resulted. The arsenicals, even when given cautiously, occasionally caused fatal reactions, but to date there has been no authenticated death from penicillin. The reactions to penicillin can be classified under a number of headings.

Systemic reactions.—So-called secondary fevers, which occurred after the first day of penicillin therapy and were not associated with typical Herxheimer reactions, have been the chief evidences of systemic reactions to penicillin therapy. In rare instances at Bellevue Hospital, spiking temperatures up to 104° F have occurred throughout the course of 7½ days of penicillin therapy of secondary syphilis. The patients had very few complaints other than fever and no other cause than penicillin could be found for the fevers, which stopped when the treatment was completed. In other patients fevers developed 4 or 5 days after beginning penicillin therapy, but in no case was treatment stopped because of these secondary fevers.

Transient albuminuria nausea and vomiting, and mild diarrhea have been reported following large amounts of penicillin especially in the treatment of subacute bacterial endocarditis, but no such reactions have been noted among the patients treated for syphilis at Bellevue Hospital.

Urticaria with or without angioneurotic edema.—At Bellevue Hospital mild or severe urticaria occurred in about 2 per cent of all patients treated with penicillin. The incidence of such reactions was less following injections of aqueous or saline solutions than of penicillin in oil and beeswax. The reaction usually appeared on the seventh to the twelfth day after beginning therapy and seldom lasted more than 4 or 5 days. In a few instances the urticaria was associated with fever and generalized pains similar to those of serum sickness. Mild or severe angioneurotic edema was observed in about 25 per cent of the cases with urticaria.

Most of our penicillin treatment schedules for early syphilis were completed within 8 days, and we found it necessary to interrupt therapy in only 2 patients they developed giant urticaria and angioneurotic edema on the seventh day after receiving six injections of 600 000 units of penicillin in oil and beeswax. When 18-day treatment schedules were used in neurosyphilis, we were able to continue penicillin in most patients in spite of urticarial reactions. The continuation of therapy failed to exacerbate the urticaria and did not appear to prolong the attack in most cases. In 5 patients under treatment for neurosyphilis, penicillin was discontinued because of angioneurotic edema and fever occurring about the tenth day of treatment. After a rest period of 10 to 12 days, injections of the same lot of penicillin were resumed in 3 of these patients without recurrence of urticaria. Antihistamine drugs were not given to these patients.

Intradermal tests with aqueous solutions of penicillin were negative in 25 patients who had severe urticarial reactions, and these findings conform with the observations of other investigators. The most severe and prolonged urticarial reaction, associated with marked edema, occurred in a patient who received penicillin in oil and beeswax. Intradermal tests with aqueous solutions of penicillin in this patient were negative, but there was a strongly positive patch test with penicillin in oil and beeswax. This was the only instance of epidermal sensitization, with positive patch tests, among our patients who had skin tests. In spite of negative skin tests, several of our patients had recurrent attacks of urticaria for some months after completing treatment with penicillin.

Pillsbury Steiger and Gibson, Curtis, Shaffer Kampmeier and others have reported control of urticarial reactions due to penicillin with antihis-

tamine drugs. Our experience with these drugs in the reactions noted at Bellevue Hospital has been disappointing In a few cases they might have relieved pruritus, but they failed to control the reactions in patients with severe angioneurotic edema. In other cases penicillin therapy could be continued without antihistamine drugs. In my experience, intravenous injections of aminophyllin have given the greatest symptomatic relief in cases of urticaria and angioneurotic edema.

Exacerbations of secondary syphilitic lesions.—A curious reaction which is unique to penicillin therapy of secondary syphilis, consists of an exacerbation of cutaneous and mucosal secondary syphilitic lesions occurring on the sixth to the tenth day after beginning penicillin therapy When treatment is completed within 7 days or less, the reaction may occur several days after the last injection of penicillin The reaction resembles an actual infectious relapse, except that dark field examinations of serum from the lesions have been consistently negative, and patients with the reaction showed no tendency to seroresistance. The reactions observed at Bellevue Hospital usually lasted from 3 to 5 days and were at times associated with fever sore throat, tender cervical nodes, and malaise. Three women who had exacerbations of secondary lesions and high fevers also had marked edema of the vulva and were acutely ill.

Similar reactions have not been noted in the treatment of secondary syphilis with antisyphilitic agents other than penicillin In many respects this phenomenon is not unlike a Herxheimer reaction, except for its duration which is longer than the usual first-day Herxheimer reaction, and as yet we have no proof that delayed Herxheimer reactions occur Nevertheless, the exacerbation of the secondary lesions suggests that a mechanism similar to that of the Herxheimer reaction may be the explanation of this, as yet unexplained, phenomenon.

Erythematous or papular skin eruptions occurring early in the course of penicillin therapy —Erythematous, papular or vesiculopapular skin eruptions appearing within the first 24 hours after starting penicillin treatment have been reported. They are believed to be the result of cutaneous sensitization by previous infection with molds or fungi. The reactions of this kind observed at Bellevue Hospital were of brief duration and seldom lasted more than 2 days, despite continuation of penicillin treatment.

Mycotic infections were present in some of the patients but not in all. Skin eruptions caused by tinea cruris were markedly exacerbated in several patients following the first injection of penicillin, but they were not

a cause for interrupting penicillin therapy As a rule, reactions of this sort have been mild and transient. Reports in the literature, however indicate that a rare patient may develop exquisite sensitivity to penicillin, and in such an individual the continuation of penicillin therapy may lead to exfoliative dermatitis.

Bullous dermatitis.—A rare but apparently definite reaction to penicillin, consisting of large bullae on the exposed surfaces of the upper extremities, has been noted on several occasions among the patients treated at Bellevue Hospital. *One of the reactions developed only after exposure to the sun, when the patient visited an ocean beach. The other* cases were associated with urticaria, but the bullae developed only on the exposed surfaces of the hands and forearms. In these patients, photosensitization may have resulted from the penicillin therapy The reaction developed between the eighth and tenth days after starting treatment. In one patient under treatment for neurosyphilis, penicillin injections were stopped for 10 days and then resumed without a recurrence of the bullae. After discharge from the hospital the patient returned on several occasions with a bullous dermatitis on the exposed surfaces of the body although he had received no additional penicillin.

Local reactions at site of penicillin injections.—Localized eruptions at the site of injection of either aqueous solutions of penicillin or of penicillin in oil and beeswax occasionally occur In a few cases observed at Bellevue Hospital, the dermatitis was quite marked, but it was not sufficiently severe in any case to cause the interruption of therapy More annoying and serious than dermatitis at the site of injections are occasional inflammations caused by injections of penicillin in oil and beeswax. Sterile abscesses within the muscle and subcutaneous tissues at the site of injections of penicillin in oil and beeswax have been reported. In all cases noted at Bellevue Hospital the swellings caused by injections of penicillin in oil and beeswax subsided without incision, and treatment was continued in all but one patient. The new slowly absorbed salts of penicillin in oil may prove less irritating than the preparations with beeswax.

METHODS OF ADMINISTERING PENICILLIN

Aqueous solutions of penicillin should be injected intramuscularly Experience has proved that there is no advantage in giving the solutions intravenously and there is the disadvantage that the penicillin is excreted even more rapidly following intravenous than intramuscular injection.

The slowly absorbed salts of penicillin in oil should also be given intramuscularly They can be given subcutaneously with equally good

therapeutic results, but subcutaneous injections are usually more painful than intramuscular injections.

Intrathecal administration of penicillin.—Following either intravenous or intramuscular injections of average doses of penicillin, the antibiotic cannot be found in the spinal fluid. As both serum and spinal fluid have the ability to inhibit the antibacterial action of penicillin, it is possible that minute amounts of penicillin in the spinal fluid are inactivated and so are not demonstrable by bio-assay. When doses of 500 000 units of aqueous solutions of penicillin are given intramuscularly penicillin has been demonstrated in the spinal fluid in all cases. But the fact that a drug is not found in the spinal fluid in no way proves that it is ineffective against central-nervous-system infections. The central-nervous-system tissues are all supplied by the blood stream, and failure to find a drug in the spinal fluid does not mean that the drug does not reach all tissues of the central nervous system.

Neurosyphilis has been treated with intrathecal injections of penicillin. The therapeutic results of this form of treatment have been reported as satisfactory. Why this should be true is not easily understood. If penicillin in the blood stream is not transferred to the spinal fluid, why should penicillin injected intrathecally be transferred to the general circulation? Obviously penicillin injected into the intrathecal space must reach the general circulation if it is to be effective against parenchymatous neurosyphilis, because the syphilitic inflammation is not confined to the meninges.

But, whatever the theoretical advantages and disadvantages of intrathecal injections of penicillin may be, clinical experience has proved that neurosyphilis can be treated effectively by intramuscular injections, and there is no reason to choose a difficult and hazardous route of administration when an easy safe, and effective procedure is available. Intrathecal injections of penicillin have, on occasion, produced serious damage in the spinal cord. I have not yet found any satisfactory reason for giving intrathecal injections of penicillin in the treatment of neurosyphilis, and the use of this route is mentioned only to advise against it.

Oral administration of penicillin.—No doubt many cases of syphilis could be treated effectively with penicillin given by mouth. Penicillin is absorbed into the blood from the gastrointestinal tract, but much larger doses are required than with parenteral injections. At Bellevue Hospital we have treated a few cases of early syphilis with penicillin given by mouth. The patients were hospitalized and treated under controlled conditions. Of 14 patients treated with 75,000 units every 3 hours for 80 doses

and followed up for 1 year 3 relapsed The oral administration of penicillin in the treatment of syphilis is not advised because, unless the patients are hospitalized, dosage cannot be controlled, and even under the best conditions one cannot place too much reliance on the constancy of absorption of penicillin from the gastrointestinal tract.

BACITRACIN

In 1945 Johnson, Anker and Meleney reported the discovery of an antibiotic in the filtrate of surface cultures of the Tracy strain of B subtilis, to which they gave the name bacitracin. At a symposium held under the auspices of the Syphilis Study Section of the National Institute of Health in April, 1948 Eagle gave a brief report on the action of bacitracin in syphilis. The antibiotic is treponemicidal, but up to the present in the treatment of syphilis it has given less satisfactory results than has penicillin. Nevertheless, according to Eagle, in experimental syphilis a marked synergistic effect has been demonstrated by combining penicillin and bacitracin therapy Further experience may show that the treatment of human syphilis can be made more effective by combining the two antibiotics. Data as to the most effective time-dose relationship of bacitracin therapy of syphilis were not available when this book was written. The investigations of bacitracin in syphilis which are now in progress will undoubtedly be reported within the next year

At present it seems unlikely that bacitracin will supplant penicillin in the treatment of syphilis, if for no other reason than that it is more toxic than penicillin With large doses, severe damage to the kidneys (tubular necrosis) has resulted in mice. Transient albuminuria has occurred in most human beings who have been treated with bacitracin, and Romansky has reported anuria and severe azotemia in a patient treated with large doses of this antibiotic.

REFERENCES

Arnold R. C Boak R Carpenter, C. M Chesney A. M Fleming, W L. Grieff B Mahoney J F and Rosahn P D A Joint Report on a Cooperative Investigation of the Efficacy of Species of Penicillin in the Treatment of Experimental Syphilis, *Am J Syph Gonor & Ven Dis* 31 469 1947

Beyer, K. H New Concept of Competitive Inhibition of Renal Tubular Excretion *Science* 105 94 1947

Coghill, R D Osterberg A E. and Hazel, G R "The Relative Effectiveness of Pure Penicillins G X, and K *Science* 103 709 1946.

Cormia, F E. and Lewis, G M. "Experimental Aspects of Sensitization to Penicillin with Special Reference to Conjoint Sensitization to Superficial Fungous Disease" *J Invest Dermat* 7 375 1946.

Curtis, A. C. "Urticaria and Allied Dermatoses," *Nebraska M J* 32:220 1947

Dowling, H. F., and Sweet L. K.: "The Absorption into and Distribution of Penicillin in the Cerebrospinal Fluid, *J Clin. Investigatio* 25 87 1946.

Dressler, C., and Dworx R. E. "Procaine Hydrochloride Intravenously in Treatment of Reactions Similar to Serum Sickness," *J.A.M.A.*, 133 849 1947

Dumoff-Stanley E. Dowling H. F and Sweet L. K. "The Absorption into and Distribution of Penicillin in the Cerebrospinal Fluid," *J Clin. Investigation* 25 87 1946.

Eagle, H. "The Therapeutic Activity of Penicillins F G K, and X against Spirochetes and Streptococci in Vitro" *J Bact* 52 81 1946

——— and Musselman A.: "The Low Therapeutic Activity of Penicillin K Relative to That of Penicillins F G and X, and Its Pharmacological Basis," *Science* 103:618, 1946.

——— and ——— "The Spirocheticidal Action of Penicillin in Vitro (Reiter Strain)" *J Bact* 47 22 1944

Editorial Board of the Monograph on the Chemistry of Penicillin "Chemical Study of Penicillin A Brief History" *Science* 105:653 1947

Fleming, A. *Penicillin Its Practical Application* The Blakiston Company Philadelphia, 1946

Gerber, A. Boldrey E. McCorkle, H. J and Warmer, H. "Effects of S barachnoid Instillations of Therapeutic Concentrations of Penicillin Solution on Central Nervous System," *J Neurosurg* 3 533 1946.

Herrell, W E. *Penicillin and Other Antibiotic Agents* W B Saunders Company Philadelphia, 1945

Johnson B. A. Anker H. and Meleney F L. "Bacitracin New Antibiotic Produced by Member of B Subtilis Group *Scienc* 102 376 1945

Kampmeier, R. H. "Use of Pyribenzamine Hydrochloride in Controlling Urticaria Due to Penicillin," *Am. J Syph., Gonor & Ven. Dis* 31 57 1947

Maloney J F Arnold, R. C. and Harris A. "Penicillin Treatment of Syphilis A Preliminary Report," *V n. Dis. Inform.*, 24 355 1943.

Moore, J E. *Penicillin in Syphilis* Charles C. Thomas, Publishers, Springfield, Ill., 1946

Olansky S Herxheimer Reactions of Relatively Small Doses of Penicillin," *J Ven. Dis Inf rm.*, 28 26 1947

Pillsbury P M. Steiger, H. P and Gibson T E. "Management (by Use of Benadryl and Pyribenzamine) of Urticaria Due to Penicillin, *J.A.M.A* 133 1255 1947

Rake, G nd Richardson A. P Pharmacology of Penicillin, in Antibiotics," *Ann New York Acad Sc* 48 143 1946.

Rammelkamp C H and Keefer, C. S. Absorption, Excretion and Distribution of Penicillin " *J Clin Investigation* 22 425 1943

——— and ——— "The Absorption, Excretion and Toxicity of Penicillin Administered by Intrathecal Injection," *Am. J M Sc* 205 342 1944

Romansky M. J "The Current Status of Calcium Penicillin in Beeswax and Peanut Oil " *Am. J Med* 1 395 1946

——— Report of a Patient Treated with Bacitracin, made at the April, 1948 Symposium on Syphilis, Washington, D C.

Scudi J V., and Antopol, W "Some Pharmacological Characteristics of Bacitracin," *Proc Soc Exper Biol. & Med* 64 503 1947

Shaffer, L. W Carrick, L. and Zackheim H. S Use of Benadryl for Urticaria and Related Dermatoses," *Arch Dermat & Syph.*, 52 243 1945

Thomas E. W Landy S. and Cooper, C. "Reactions to Penicillin Therapy for Syphilis," *J Inv st Dermat* 10 77 1948.

——— Lyons R. H. Romansky M. J Rein C. R. and Kitchen D K. "Newer Repository Penicillin Products," *J.A.M.A* 137 1517 1948

Tompsett R. Schultz, S. and McDermott W "Relation of Protein Binding to Pharmacology and Antibacterial Activity of Penicillins X, G Dihydro F and K " *J Bact* 53 581 1947

Tucker, H. A., and Farmer, T W Penicillin in Cardiovascular Syphilis (Includes a Report on Herxheimer Reactions) *Arch. Int Med* 80 322, 1947

Turner, T B Cumberland, M and Li Huan Ying "Comparative Effectiveness of Penicillins G F K, and X in Experimental Syphilis as Determined by a Short in Vivo Method, *Am. J Syph. Gonor & Ven. Dis.*, 31 476, 1947

CHAPTER 7

PRINCIPLES UNDERLYING ANTISYPHILITIC TREATMENT

THE principles underlying the treatment of syphilis can be summarized as follows

1. Treatment should be completed in the shortest time consistent with good results.
2. Treatment should be as safe as possible.

It is my intent to evaluate modern antisyphilitic therapy in the light of these principles, but, before doing so, it is necessary to review what was accomplished by therapy before the introduction of penicillin. It is futile to condemn a new therapy simply because it is not uniformly successful. A fair evaluation demands that we compare the effectiveness and safety of the new therapeutic method with all other possible methods of treatment and the evaluation must take into account every relevant factor especially the control of the disease from a public health point of view With the above thoughts in mind, this chapter is written to survey the various methods used to treat syphilis in the past decade and to give general guides for the use of penicillin.

RAPID ANTISYPHILITIC THERAPY CONTRASTED WITH PROLONGED TREATMENT

When Ehrlich introduced arsphenamine, it was hoped that a quick method of curing syphilis would result. Disillusionment followed when it was found that syphilis was seldom cured by a few injections of the drug, and that the drug was too toxic for intensive use. As a result, the routine therapy of syphilis became a prolonged program of weekly injections lasting anywhere from 1 to many years. The usual procedure was to give alternate courses of mercury or bismuth and arsenicals, although it was not unusual for patients to receive weekly injections of both bismuth and an arsenical when the latter was well tolerated. Previous experience with

RAMMELKAMP C. H and KEEFER, C. S Absorption, Excretion and Distribution of Penicillin" *J Clin. Investigation* 22 425 1943

——— and ——— "The Absorption, Excretion and Toxicity of Penicillin Administered by Intrathecal Injection," *Am. J M Sc* 205 342 1944

ROMANSKY M J "The Current Status of Calcium Penicillin in Beeswax and Peanut Oil" *Am. J Med.*, 1 395 1946

——— Report of a Patient Treated with Bacitracin made at the April, 1948 Symposium on Syphilis, Washington, D C.

SCUDI, J V., and ANTOPOL, W "Some Pharmacological Characteristics of Bacitracin," *Proc Soc Exper Biol. & Med* 64 503 1947

SHAFFER, L. W CARRICK, L. and ZACKHEIM H S. Use of Benadryl for Urticaria and Related Dermatoses, *Arch. Dermat & Syph.*, 52 243 1945

THOMAS E. W LANDY S and COOPER, C. "Reactions to Penicillin Therapy for Syphilis," *J Invest Dermat* 10 77 1948.

——— LYONS R. H ROMANSKY M. J RIIN C. R. and KITCHEN D K. "Newer Repository Penicillin Products," *J.A.M.A* 137 1517 1948.

TOMPSETT R. SCHULTZ, S and McDERMOTT W Relation f Protein Binding to Pharmacology and Antibacterial Activity of Penicillins X, G Dihydro F and K" *J Bact* 53 581 1947

TUCKER, H. A. and FARMER, T W Penicillin in Cardiovascular Syphilis (Includes a Report on Herxheimer Reactions)" *Arch Int Med.*, 80 322, 1947

TURNER, T B CUMBERLAND M and LI HUAN YING Comparative Effectiveness of Penicillins G F K, and X in Experimental Syphilis as Determined by a Short in Vivo Method," *Am. J Syph., Gonor & Ven. Dis.*, 31 476 1947

The investigations of Chargin, Leifer and Hyman proved beyond doubt that arsenoxide in effective doses is much less toxic than neoarsphenamine. Their work also stimulated others to try various types of rapid treatment and finally led to the establishment of numerous rapid treatment centers for syphilis by the United States Public Health Service.

As previously noted, massive arsenotherapy even with arsenoxide, was attended with serious toxic effects in some cases, and its therapeutic advantages had to be weighed against its potential danger. At Bellevue Hospital we found it possible to continue rapid treatment of early syphilis in periods of 10 days or less only by cutting the previously required dose of arsenoxide in half and giving four bouts of fever induced by typhoid vaccine. Despite this dosage reduction, treatment was not without serious danger in rare cases, and it caused much discomfort to patients and was a source of anxiety to the physicians in charge. But, even if a 6- to 10-day schedule of massive arsenotherapy should have proved too toxic for general adoption, its trial opened the way to shortening the period of treatment of all types of syphilis. By 1942 the United States Army and Navy had adopted a 6 months' schedule of treatment for early and late syphilis, except for neurosyphilis which was treated with fever therapy. The results of the 6 months' schedule were apparently superior to those obtained when less intensive therapy was given for 1 to 2 years. Sternberg and Leifer reported excellent results with this type of therapy.

From the public health point of view the trial of massive arsenoxide therapy of early syphilis, with or without induced fevers, was worth the risk involved. For the first time in America, large numbers of clinic patients received adequate treatment of early syphilis. Rapid therapy of early syphilis failed to prevent relapses or reinfections in 15 to 20 per cent of patients, but re-treatment with the same schedule of therapy was usually successful.

Comparative results of older methods of routine treatment and rapid treatment of early syphilis.—In 1940 Padget reported on the long-term results of the older forms of treatment of early syphilis at Johns Hopkins Hospital. The patients included in the report were observed for 5 to 10 years after termination of treatment. Of the 551 patients observed for at least 5 years, regardless of the type or amount of treatment received, 65.7 per cent had negative STS and showed no clinical evidence of syphilis. Of the remaining patients, 14.9 per cent had only positive STS, 12.3 per cent had neurosyphilis, and 7.1 per cent had various late manifestations of the disease other than neurosyphilis. This report came from one of the best syphilis clinics in America, with personnel sufficient to

carry out clinical studies, treatment, and follow-up observations. Consequently the results of Padget s long-term observations were probably better than the average obtained in most clinics by the older methods of routine therapy

At Bellevue Hospital, by March 1 1948 635 patients, given one or more courses of rapid treatment of early syphilis with arsenoxide or arsenoxide and fever had been observed from 4 to 8 years. Except for a slightly shorter period of follow-up the Bellevue Hospital series is comparable to that reported by Padget and probably represents a larger

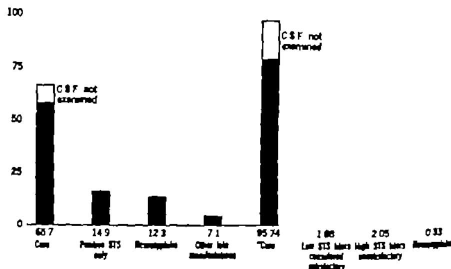


FIG. 33. Comparison of final outcome in 551 patients treated for early syphilis at Johns Hopkins Hospital, followed p for 5 t 10 y ars, and 635 patients treated for early syphilis t Bellevue Hospital, followed p for 4 t 8 years. The Johns Hopkins Hospital pat ents reported by Padget were treated by the older conventional therapy and many received inadequate therapy The Bellevue Hospital patients were given rapid arsenotherapy or arsenotherapy combined with fever and bismuth.

sample of the total group treated than the one reported from Johns Hopkins Hospital

Of the 635 patients in the Bellevue Hospital group, 608 (95 74 per cent) were clinically well and seronegative when last observed Of the remaining 27 patients, 12 (1 88 per cent) had either complement fixation or Kahn titers of 2 or 3 units and normal spinal fluid findings 15 (2.38 per cent) had Kahn titers of 8 to 128 units and were considered unsatisfactory most of them having been re-treated within recent months (Fig 33) Of the entire group of 635 patients, 100 (15 7 per cent) had not had spinal fluid examinations more than 1 year after their last treat

ment. All but 2 of the remaining 535 patients had normal spinal fluids when last examined. So far we have found no abnormal spinal fluids 1 year or more after rapid treatment of early syphilis among patients who had become and remained seronegative. Of the 535 patients who had spinal-fluid examinations more than 1 year after treatment, 292 had repeated spinal-fluid examinations from 2 to 8 years after treatment. The 2 patients who still had abnormal spinal-fluid findings for syphilis when last seen also had strongly positive STS of the blood. They were patients who lapsed from follow up for 2 years or more and were found to have abnormal spinal fluids when they returned for examination but neither had clinical signs of neurosyphilis. About 14 per cent of the 535 patients who had normal spinal-fluid examinations 1 or more years after treatment had had abnormal findings at the time of their original treat ment or at the time of re-treatment. All patients who had abnormal spinal fluids at any time have had repeated spinal-fluid examinations at 6- to 12 month intervals after treatment. At the time of their first rapid treatment, 4 patients in this series had severe symptomatic neurorecur rences following previous inadequate ambulatory treatment for secondary syphilis. Following rapid treatment, all recovered without sequelae.

Thus, after an observation period of 4 to 8 years, 635 patients who had one or more rapid arsenical treatments of early syphilis have no physical evidence of syphilis 608 (95 74 per cent) are completely seronegative, and an additional 12 (1.88 per cent) are considered satisfactory in spite of weakly positive STS 13 (2 05 per cent) have strongly positive STS only and most of them have recently been re-treated only 2 (0.33 per cent of 635 or 0.37 per cent of the 535 patients who had spinal fluid examinations 1 or more years after treatment) have abnormal spinal fluids. Of the 635 patients, 516 were treated only once 119 had one or more re-treatments, 98 ha ing been re-treated once, 17 twice, 3 three times, and 1 four times.

Judging from previous experience, less than 20 per cent of the patients who received massive arsenotherapy for early syphilis at Bellevue Hospital would have received, in the average ambulatory clinic, as many as 20 injections of arsenoxide and 20 of bismuth within 1 year after the diag nosis had been made. True, we were able to observe for more than 4 years only 30 per cent of the total number of patients given rapid arsenical treatment, but about 60 per cent were followed for at least 2 years. Re infections unquestionably accounted for many of the re-treatments in the series given rapid treatment, but reinfections were more common follow ing successful routine therapy of early syphilis than is generally recog

nized. In the series of patients given massive arsenotherapy at Bellevue Hospital, more than 100 were treated for probable reinfections after previous prolonged therapy of primary and secondary syphilis. From the *public health point of view the advantages of rapid treatment of early* syphilis have been well established

Rapid arsenical treatment of late syphilis.—Less is known about the effects of rapid arsenotherapy of late syphilis than of early syphilis. Intensive treatment with arsenical drugs was not suitable for cardiovascular syphilis or late syphilis of the liver but about 150 cases of latent syphilis and a few patients with skin gummas or bone syphilis received rapid arsenotherapy combined with four bouts of fever at Bellevue Hospital. So far as we have been able to determine, the therapeutic results were as satisfactory as after prolonged treatment with weekly or semiweekly injections.

Before penicillin became available, patients with active neurosyphilis were routinely treated at Bellevue Hospital with 8 malarial febrile paroxysms followed by 10 daily injections of 0 06 gm arsenoxide The results of this treatment were markedly superior to prolonged therapy with pentavalent or trivalent arsenicals and bismuth.

Over 50 per cent of the patients treated for active neurosyphilis at Bellevue Hospital with either malaria or penicillin had had from a few to several hundred injections of heavy metals and arsenical drugs in previous years. One patient with general paresis had been treated more or less continuously at weekly intervals, for 11 years. The idea was apparently prevalent that the longer syphilis was treated with weekly injections of bismuth and/or arsenical drugs, the better would be the results. My experience has convinced me that this idea was erroneous. I have found that if neurosyphilis was not controlled by weekly injections of reasonably adequate doses of arsenical drugs and bismuth in 1½ years, further treatment of the same kind failed to control the disease. I am also of the opinion that intensified therapy with arsenical drugs and bismuth will arrest late syphilis in 3 to 6 months if it fails to do so, further treatment of the same kind will accomplish very little. Although the statistical evidence regarding shortened periods of therapy of late syphilis is inadequate, such data as are available indicate that with three injections a week, 4 to 6 months of treatment with arsenicals and bismuth give as good results as less intensive treatment over a period of 2 years.

The trend toward more intensive and shortened periods of antisyphilitic therapy was, I believe, in the right direction, but, when from 1.2 to 1.8 gm arsenoxide were given in less than 3 months, the incidence of

undesirable reactions was significantly increased. Consequently the discovery that penicillin was an effective antisyphilitic agent came as a great relief to those of us who struggled with this problem.

PRINCIPLES UNDERLYING PENICILLIN TREATMENT OF SYPHILIS

Although optimum time-dose schedules of penicillin therapy of syphilis have not yet been finally determined, the experience of the past 4 years permits some general conclusions which can serve as guides in the treatment of the various stages of syphilis. No claim is made that the conclusions are final, but they are based on data which are probably more reliable than most of the previous statistics regarding antisyphilitic treatment with heavy metals and arsenicals. To appraise penicillin in syphilis, it will be necessary to review its action not only in human syphilis but also in experimental syphilis and against other bacteria than the T pallidum.

Activity of penicillin against various bacteria.—Numerous observers have found that penicillin-sensitive bacteria in vitro are killed by penicillin only when multiplying. Thus, in vitro the multiplication of penicillin-sensitive bacteria is completely inhibited by penicillin, and all but a few organisms are destroyed. On re-culture, the few surviving organisms, after a lag phase, begin to divide. Presumably the activity of penicillin against these organisms is the same in vivo as in vitro. Thus, McDermott suggests that few infections are completely eradicated by antibacterial agents, and that the few surviving organisms are inhibited or destroyed by the developing resistance of the host. This may be true of acute infections, but we have no proof that it is true of syphilis which requires months for the host to develop sustained, demonstrable, increased resistance to the infection. Nevertheless, the possibility that penicillin is inactive against nondividing treponemes is of sufficient interest to raise some points for speculation.

Theoretical considerations of activity of penicillin in treatment of early syphilis.—*The action of penicillin against virulent T pallidum in vitro* cannot be determined But, if we assume that, in vivo, penicillin is effective against virulent treponemes only during the phase of multiplication, three theoretical possibilities regarding penicillin treatment of early syphilis can be formulated (1) The treponemes may all be metabolically active at the time of treatment, and the infection may be completely eradicated by therapy; (2) a few organisms may be in an inactive phase at the time of treatment, and at varying periods thereafter they may

revive and multiply causing a relapse (3) a few organisms may survive for varying periods after treatment, only to be finally destroyed by the resistance of the host.

The first of these possibilities will be discounted by those who believe that antibacterial drugs or antibiotics rarely destroy 100 per cent of the bacteria in an infection and that the few surviving organisms are held in check or finally destroyed by the immune mechanisms of the host. Whether or not this belief is true in the treatment of early syphilis is unknown But, even if a few treponemes survive for varying periods after penicillin treatment of early syphilis, *I doubt that they live for long* periods in the body without reviving and multiplying

The second possibility (that dormant treponemes survive after treatment and later begin to divide) is supported by the occurrence of relapses following penicillin treatment of early syphilis. As previously noted, most relapses of early syphilis occur within 9 months after therapy The time when clinical or serologic manifestations of a relapse become evident after treatment depends on at least three undeterminable factors (1) the number of treponemes surviving after treatment (2) the time during which the surviving organisms remain dormant without dividing and (3) the rate of multiplication after they begin to divide. Assuming that only a few organisms survive treatment, from 4 to 8 weeks may elapse after the organisms begin to multiply at a normal rate before the relapse becomes serologically or clinically demonstrable. If we accept the theory that penicillin is inactive against nonmultiplying treponemes, additional penicillin therapy during the stage when the organisms are not dividing should have no effect. This theory might be used to explain the observation that a second course of penicillin therapy has had no effect on low STS titers which persist for many months after treatment. I question the validity of this argument because we have no evidence that the prolonged presence of small amounts of reagin is due to the continued presence of treponemes in the body and past experience has proved that treatment with bismuth and arsenicals, as well as with penicillin, has failed to hasten the reversal of low STS titers following rapid treatment of early syphilis. Probably relapses could be prevented by repeated courses of penicillin at intervals of 2 to 3 months. Such therapy is impractical, however because the majority of patients would receive unnecessary treatment, and it is impossible to know in advance at what intervals treatment should be given to prevent relapses in all patients. With the possible exception of syphilis complicated by pregnancy it seems more practical to wait for evidences of relapse and then re-treat the small percentage that will require it

The third possibility (that a few inactive treponemes survive for long periods following rapid treatment of early syphilis and are finally destroyed by the resistance of the host) could explain the prolonged persistence of low STS titers, which eventually become negative, in patients who have had rapid treatment of early syphilis. This theory however is less convincing than might appear on first impression. There is no evidence that, following treatment of early syphilis, the body develops increased resistance to treponemes during a long period of inactive infection with a few dormant treponemes. The persistence of reagin is not evidence of increased resistance to a syphilitic infection. We know that the presence of reagin in rabbits confers no immunity against reinfection. Almost certainly the same statement can be made of reagin in human beings. Following rapid treatment of early syphilis, many patients have undoubtedly been reinfected while the STS were still positive. Consequently it is improbable that a few nonmultiplying treponemes in the body can appreciably stimulate the defense mechanism of the host, regardless of whether reagin is or is not still present in the blood serum. Infectious relapses prove that the presence of dormant treponemes in the body fails to produce a refractory state toward early lesions. If "resting" treponemes were the cause of prolonged positive STS in patients who finally became seronegative 2 or more years after rapid treatment, we should have observed more serologic or infectious relapses in these patients than have been noted at Bellevue Hospital. Landy who is one of the most careful and thorough observers of syphilis I have known, believes that the few patients who had low STS titers at Bellevue Hospital and developed new infectious lesions 2 years or more after rapid treatment of early syphilis were reinfected. The histories and the clinical findings support this belief New chancres without a concomitant rise in STS titers from previous levels were noted in several patients with prolonged positive STS more than 2 years after treatment of an original infection. If one chooses to believe that the chancres in these patients were evidences of superinfection, it still follows that the patients failed to develop an increased resistance to T pallidum. As a matter of fact, there is every reason to believe that such increased resistance as has been developed by the host at the time of treatment of early syphilis rapidly disappears following treatment.

Obviously we do not know how long treponemes can remain in the body without multiplying following rapid treatment of early syphilis. It may be that a few treponemes survive after the completion of treatment and subsequently die without multiplying but there is no reason to believe

that they are the cause of prolonged positive STS after treatment. Regardless of theory clinical experience has proved that re treatment of patients solely because of positive STS following rapid treatment of early syphilis, in the absence of serologic or clinical evidences of relapse, has failed to hasten the reversal of low STS titers to negative. This fact has great practical importance and cannot be discounted on theoretical grounds.

Theoretical considerations of activity of penicillin in latent syphilis.— If it is true that penicillin is inactive against nonmultiplying treponemes, Moore has postulated that, in that case, penicillin may be of minimal or no value in latent syphilis. This possibility is logical only if we assume that treponemes are in an inactive metabolic state throughout latent syphilis. As a matter of fact, we do not know the metabolic status of T pallida in latent syphilis. In this stage treponemes are not found in enormous numbers as in early syphilis, but this gives us no right to assume that they do not divide. The rate at which the organisms multiply in latent syphilis may be decreased and the mortality rate increased because the host has had the opportunity to develop resistance to the organisms, but it is improbable that T pallidum remains in the body without dividing for even a year unless it has a life cycle with a resting form. In late symptomatic syphilis, as in latent syphilis, the number of treponemes in the body is much smaller than in early syphilis. Therefore, late syphilitic inflammation is less dependent on the number of treponemes than on the reactivity of the body tissues to the syphilitic virus. Treponemes are found with great difficulty in skin gummas yet the reaction of the sensitized skin may be both severe and prolonged. Thus, the difference between latent and symptomatic late syphilis probably has little to do with the status of the treponemes. Certainly we cannot assume that the organisms in latent syphilis are metabolically inactive.

The only reliable means of evaluating the results of therapy in latent syphilis are lifetime observations of large numbers of patients. So far such long-term observations of large series of patients have been impossible, but, in spite of this fact, the available evidence indicates that latent syphilis can be permanently arrested in a very high percentage of cases with moderate amounts of good antisyphilitic treatment. Serologic tests for syphilis following therapy of latent syphilis are unsatisfactory criteria of the results of treatment, but they afford some valuable information. Usually a gradual but definite fall in quantitative tests occurs within 1 or 2 years following penicillin therapy of latent syphilis. Presumably this observation indicates that the stimulus to reagin formation was defi-

nitely lowered. Whether or not the infection was eliminated by treatment cannot be determined, but much experience with heavy metals and arsenical drugs and more limited experience with penicillin have shown the futility of attempting to reverse positive STS to negative in well treated latent syphilitics whose quantitative STS show no evidences of sustained rises from previous levels.

We know that many untreated patients with late latent syphilis will never be seriously troubled by the disease. But as we have no way of measuring the activity of the infection it is safer to treat latent syphilis than to observe it without treatment. There is no reason to believe, however that latent syphilis requires more penicillin to prevent relapse or progression than does late syptomatic syphilis or even secondary syphilis.

Theoretical considerations of activity of penicillin in late symptomatic syphilis including all types of neurosyphilis.—Late lesions of syphilis, as a rule, have healed rapidly following penicillin. From the available reports, late syphilis of the skin and bones has responded well to penicillin therapy with the exception of two cases reported separately by Hill and Hahn. Hill reported a gumma of the nasal septum and hard palate which failed to improve after 2 400 000 units of penicillin but healed with malaria therapy Hahn reported a gumma of the penis which responded to Mapharsen but not to penicillin. These exceptions are difficult to explain on any other basis than that some strains of treponemes are more resistant to penicillin than others. It must be remembered, however that in past years reports have been made of occasional early and late cutaneous syphilides which failed to repond to arsenical drugs, and it is not surprising that similar incidents have occurred with penicillin therapy

In a recent article on treatment failures in late syphilis following penicillin therapy Reynolds reported progression of neurosyphilis after penicillin in several cases and cautioned against the assumption that the therapeutic activity of penicillin in late syphilis is comparable to that in early syphilis. A few exceptions to a rule, however cannot discredit the well-documented fact that, so far penicillin has proved unusually effective in the treatment of late syphilis in both experimental animals and human beings. Patients with neurosyphilis have relapsed or progressed after malaria therapy as well as after penicillin, but the percentages of such failures have been low after both types of treatment. In my experience, penicillin has proved superior to both arsenicals and bismuth in the treatment of late symptomatic syphilis.

At Bellevue Hospital we have treated and observed for more than 2 years 26 cases of skin gummas and bone syphilis that healed promptly

cates that syphilitic infection in rabbits is eradicated during or shortly after curative doses of penicillin.

The results of penicillin therapy of syphilis in rabbits provide a useful background for penicillin therapy of syphilis in human beings, in spite of the fact that in rabbits the disease is much more easily cured than in human beings. In the experimental animal, and in man the important problem is to determine the optimum time-dose relationship of penicillin therapy of syphilis.

Time-dose factors in therapy of experimental syphilis with aqueous solutions of amorphous penicillin.—In the treatment of syphilis in rabbits with aqueous solutions of amorphous penicillin, Eagle, Magnuson, and Fleischman studied the effect of three variables on the curative dose. A summation of their findings follows

1. Regardless of the time interval between individual injections, the greater the number of injections, the less the total amount of penicillin necessary for cure. Thus, to cure experimental syphilis with 4 to 8 injections required from 60 000 to 80 000 units per kilogram by increasing the number of injections to 50 and also increasing the period of therapy the curative dose was reduced to as little as 360 units per kilogram.
2. When the duration of treatment was kept constant at 4 days, the total curative dose of penicillin depended on the number of injections given. With four injections (one daily) the dose which cured 50 per cent of the rabbits (CD 50) was 50,000 units per kilogram with 20 injections (five daily) the CD 50 was reduced to 1 600 units per kilogram.
3. When the total number of injections was held constant (at 16) the curative dose depended on the interval between injections. Better results with lower curative doses were obtained when injections were given every 4 to 8 hours than when given every 1 to 2 hours. When injections were given every 24 hours, thereby extending the treatment period to 16 days, the curative dose was much the same as when injections were given every 4 to 8 hours.

The results of these experiments show that syphilis in rabbits can be cured by a wide variety of time-dose schedules of penicillin therapy Relatively small doses of penicillin, given at 4- to 8-hour intervals over a period of 4 days, proved to be the most satisfactory To cure rabbits in a single day the total dose of penicillin had to be increased 200 times. It would appear therefore, that prohibitive amounts of penicillin in aqueous

solution would probably be needed to cure early syphilis in human beings in a single day

In experimental syphilis, giving aqueous solutions of amorphous penicillin every 3 hours for 4 days, Arnold and coworkers found the CD 95 to be about 3,500 units per kilogram. With the same schedule, Fleming and Wolf found the CD 95 for early syphilis in rabbits to be 2,000 units per kilogram, and for late syphilis the CD 95 was also about 2,000 units per kilogram. Thus, late syphilis in rabbits is apparently no more difficult to cure with penicillin than primary syphilis. It should be noted, however that Eagle and his associates found that, when rabbits were treated within 4 days after inoculation, much smaller doses of penicillin were required for cure than when a chancre had already developed.

Results of treatment of experimental syphilis with penicillin in oil and beeswax.—Using amorphous calcium penicillin in oil and beeswax to treat experimental syphilis in rabbits, Magnuson and Eagle found the CD 50 of a single injection to be 50 000 units per kilogram. With daily injections for 4 days the CD 50 was 3,500 units per kilogram; with two daily injections for 8 days the CD 50 was 800 units per kilogram and with two injections a week for 8 weeks the CD 50 was 1,500 units per kilogram.

Thus, with slowly absorbed preparations of penicillin as with aqueous solutions, extending the period of treatment to at least 4 days greatly lowered the total amount of penicillin required to cure at least 50 per cent of the rabbits. Continuing therapy beyond 4 days provided cures with even less total dosage of penicillin in oil and beeswax than when injections were given for only 4 days.

No reports have as yet been made on treatment of experimental or human syphilis with procaine penicillin G in oil, but there is every reason to believe that the results of therapy with this preparation will be equally as good as, if not better than, those obtained with penicillin in oil and beeswax.

Synergistic effect of penicillin and arsenoxide in experimental syphilis.—Eagle and his associates found that concurrent intravenous injections of arsenoxide and intramuscular injections of penicillin made it possible to cure syphilis in rabbits with much less than half the CD 90 of both drugs. The combination of arsenoxide and penicillin, however has not given significantly better results than 2,400 000 units of penicillin alone in the treatment of early syphilis in man.

Effect of fever combined with penicillin in experimental syphilis.—The experiments of Eagle and his coworkers indicate that in rabbit syphilis

the penicillin CD 50 and CD 90 can be greatly reduced by a single 10-hour session of fever So far the experience with combined penicillin and fever therapy of early syphilis in human beings has not been impressive. Possibly early syphilis could be cured in a high percentage of cases within 2 days by a combination of fever arsenoxide, and large doses of aqueous solutions of penicillin but such therapy is impractical and involves unnecessary risk and discomfort to patients. Furthermore, fever therapy should be carried out only in a hospital, and this would be undesirable for many patients with syphilis.

PENICILLIN IN HUMAN SYPHILIS

Most of the clinical research in penicillin therapy of early syphilis at Bellevue Hospital has been with varying doses of penicillin alone, or with penicillin combined with arsenoxide in a 7½-day period. The Central Statistical Unit at Johns Hopkins Hospital, originally established by the Subcommittee on Venereal Diseases of the National Research Council and subsequently sponsored by a similar Committee of the National Institute of Health is still evaluating long-term results of various schedules of treatment given over periods of 4 to 15 days.

Treatment of early syphilis with aqueous solutions of penicillin.— With aqueous solutions of penicillin the optimum total dose, when individual injections were given every 2 to 6 hours for 7½ days, was about 2 400 000 units. When the dose was increased to 4 000,000 or 5,000,000 units in the same period of time, there was no significant increase in satisfactory results over those obtained with 2 400 000 units. When at least 1,200,000 units of penicillin were given in 7½ days, the addition of eight daily injections of 0 04 gm arsenoxide and five injections of 0.2 gm bismuth subsalicylate in oil failed to give significantly better results than 2 400 000 units of penicillin alone

As will be shown in detail in Chap. 9 the cumulative "failure" rates for various schedules employing 2,400 000 to 4,800 000 units of penicillin alone or penicillin combined with other antisyphilitic drugs are very similar At Bellevue Hospital the cumulative "failure rates (including infectious relapses, reinfections, and serologic relapses as well as seroresistant cases) have been about 20 per cent in early syphilis for a follow-up period of more than 1 year Even higher "failure" rates have been reported by the Central Statistical Unit. Mahoney and coworkers of the Venereal Disease Research Laboratory at Marine Hospital, Staten Island, on the other hand, have reported successful results in 95 per cent of patients with early syphilis treated with 40 000 units of penicillin every

2 hours for 85 injections and followed up for 1 year or more. Various reasons have been suggested for the discrepancy between the findings of the Central Statistical Unit and those of the Venereal Disease Research Laboratory The most plausible explanation, in my opinion, is the probability that fewer patients in the series treated in the Marine Hospital were reinfected. Most of them were sailors who returned to sea immediately after treatment as a result they were less liable to reinfection by their previous contacts. It is also true that most of the patients treated by Mahoney and his coworkers had primary syphilis, while the majority of the patients in the other reported series had secondary syphilis. But, in our experience at Bellevue Hospital, there has been no significant difference in the cumulative "failure" rates of patients treated for seropositive primary syphilis and of those treated for secondary syphilis except in the case of white males. About 70 per cent of our cases were Negroes.

At the April, 1948, symposium of the Syphilis Study Section of the National Institute of Health, Mahoney reported satisfactory therapeutic results in a high percentage of patients treated with 200 000 units of penicillin G in aqueous solution every 2 hours for 3 days—a total of 7,200,000 units. This schedule was based on experiments in rabbits, which proved that much larger doses of penicillin were required to cure syphilis when the treatment period was shortened to less than 4 days.

Since April, 1946 the United States Army has treated seronegative primary syphilis with 100 000 units of penicillin every 3 hours for 60 doses, and seropositive primary and secondary syphilis with 100 000 units every 3 hours for 80 doses. I have no data on the results of this therapy It is probable that prolonging the period of therapy of seropositive primary and secondary syphilis to 10 or more days will give better therapeutic results than when treatment is confined to 7 or 8 days, but the data of the Central Statistical Unit do not show any significant advantage in increasing the total dosage of penicillin beyond 2,400 000 units in 8 or 10 days.

Treatment of early syphilis with penicillin in oil and beeswax (POB)—The results of therapy of early syphilis with 2 400 000 to 4,800,000 units of penicillin in oil and beeswax (POB) regardless of whether injections were given once or twice a day for 8 days, have been similar to those obtained with 2 400,000 to 4 800 000 units of penicillin in aqueous solution in 7½ days.

As slowly absorbed preparations of penicillin permit ambulatory treatment of syphilis, it is important to learn whether or not better therapeutic results can be obtained by prolonging the period of therapy of early

syphilis beyond 8 days. The Syphilis Study Section of the National Institute of Health is now investigating various schedules of POB therapy prolonged for periods of 2 to 8 weeks. At Bellevue Hospital for the past 6 months, we have treated early syphilis with 600 000 units of POB by a single daily injection for 15 days. The period of follow-up of the patients treated with this schedule is too short for any conclusions at this time, but, so far the results have been much better than those obtained with an 8-day POB schedule. It seems probable that prolonging treatment to at least 15 days will prove more effective than an 8-day schedule, but prolonging the period of treatment does not necessarily mean that the total dose of penicillin must be increased. Giving 600 000 units of POB daily for 15 days may be wasteful of penicillin equally good results might be obtained with 300 000 units daily for 15 days, or 600 000 units every other day for eight injections. In fact, while writing this chapter I learned from Chargin Sobel Rein, and Rosenthal that they had prepared a report, not yet published, on the treatment of 153 cases of early syphilis with daily injections of 300 000 units of POB for 16 days with significantly better results than those reported for 600 000 units daily for 8 days.

Procaine penicillin G in oil and aluminum monostearate.—A single injection of 300,000 units of POB gives demonstrable blood concentrations for at most 20 to 30 hours. A similar dose of procaine penicillin G in oil and aluminum monostearate gives demonstrable blood concentrations for at least 4 days. Therefore, the way is opened for a much wider range of time-dose relationships than was previously possible. Daily injections of procaine penicillin in oil and aluminum monostearate would seem to be unnecessary and wasteful. Injections of from 300 000 to 600, 000 units need not be given more frequently than every 4 days, and possibly injections at weekly intervals would be sufficient. When large doses of 1 000,000 to 3 000 000 units were given, blood concentrations of penicillin were obtained for 5 days in most cases and for 7 or more days in some cases. In view of this delayed absorption it is now conceivable that early syphilis can be cured with a single treatment of from 2,000 000 to 3 000 000 units of procaine penicillin in oil and aluminum monostearate in as high a percentage of cases as with daily injections of 300,000 units of POB for 8 days.

Possible cure of early syphilis with a single treatment.—If early syphilis could be cured in a high percentage of cases by a single treatment, it would have many advantages from a public health point of view Past experience in clinics has proved the difficulty of keeping patients

with early syphilis under regular treatment on an ambulatory basis. Therefore, at Bellevue Hospital, we recently gave a patient with secondary syphilis four simultaneous injections of 750 000 units of procaine penicillin in oil and aluminum monostearate at four different sites in the buttocks. The injections were made in rapid succession, and no further treatment was given. The patient had no pain from the injections and no untoward reactions of any kind. Following this single treatment, blood concentrations of 0.03 or more units of penicillin were found for 7 days. Although no report can be made at this time about the ultimate effectiveness of this treatment, it is reasonable to believe that a single treatment which gives demonstrable blood concentrations of penicillin for 7 days should be as effective as treatment with aqueous solutions every 3 hours for 7½ days.

Further experience may prove that procaine salts are too toxic in such large doses, but other penicillin salts may be synthesized which will be less toxic. At present it seems that procaine penicillin can be used in large doses with safety. Procaine hydrochloride in doses of 200 to 250 mgm has been given intravenously to alleviate pain and has proved valuable in serum sickness. As much as 2 gm procaine hydrochloride has been injected subcutaneously for local anaesthesia. Three million units of procaine penicillin contain 1.2 gm procaine, which is absorbed slowly as is the penicillin. From our present knowledge, the chief contraindication to large doses of procaine penicillin would seem to be serious liver disease, because procaine is normally detoxified rapidly in the liver.

Other possible treatment schedules with procaine penicillin in oil and aluminum monostearate.—If as seems probable, a 15-day treatment period is found to give better results than one of 8 days, two treatments, each consisting of 1 000,000 to 2 000 000 units of procaine penicillin in oil and aluminum monostearate given a week apart should give the same results as daily injections of 300 000 units of POB for 15 days. Other possible schedules of therapy with very slowly absorbed penicillin preparations would be injections of 600,000 units every 4 days for four to six injections, or weekly injections of 1,200 000 units for 2 to 4 weeks. Obviously we now have a choice of a wide range of time-dose relationships in penicillin therapy of syphilis, schedules can be chosen to suit the convenience of both patient and physician. It seems unlikely however that prolonging therapy beyond 4 weeks will be necessary.

It is, of course, possible that higher blood concentrations of penicillin are needed to destroy some strains of treponemes than are provided by the very slowly absorbed preparations of penicillin. So far however we

superior to any previously known antisyphilitic agent including malaria therapy It may be found that an occasional patient with neurosyphilis will require fever therapy but in our experience thus far at Bellevue Hospital, such instances are rare. About 90 per cent of our patients, whose spinal-fluid tests showed an active syphilitic process in the central nervous system, have had satisfactory spinal-fluid tests more than 1 year following penicillin therapy this compares with an approximately 85 per cent good response in a more or less similar group treated with malaria.

Most of our patients with neurosyphilis were treated with 40,000 units of penicillin in aqueous solution every 3 hours for 150 doses. This represents a treatment period of almost 19 days. More recently we have been treating neurosyphilis with 15 daily injections of 600 000 units of POB. No report of the results of the latter schedule of therapy can be given at this time, but there is every reason to believe that the results will be comparable to those obtained with aqueous solutions. Possibly equally good results could be obtained with less frequent injections of procaine penicillin G in oil and 2 per cent aluminum monostearate, for example, two or three injections a week for 3 to 4 weeks. From the data now available, neurosyphilis can be well treated with 6 000,000 units of penicillin given over periods of 3 to 4 weeks. Patients whose spinal-fluid tests indicate a relapse of neurosyphilis following treatment should be re treated with at least 9 000 000 units of penicillin over a period of at least 3 weeks. So far at Bellevue Hospital we have encountered only one patient with neurosyphilis whose spinal-fluid findings indicated a continuing activity of the infection, or a relapse, following a second course of penicillin therapy

In syphilis associated with pregnancy penicillin therapy has been much more satisfactory than any previous form of treatment. Congenital syphilis has been prevented in from 95 to 98 per cent of offspring of pregnant women treated with 3 000 000 to 6 000 000 units of penicillin, regardless of whether the woman had early or late syphilis. At Bellevue Hospital most of the pregnant women were treated with 40 000 units of penicillin in aqueous solution every 3 hours for 100 doses. A smaller series received 600 000 units of penicillin in oil and beeswax for 8 days with equally good results.

Conclusions.—With occasional exceptions in individual cases, all types of late syphilis can be effectively treated with penicillin in doses ranging from 4 000 000 to 9 000 000 units. The available data indicate that even better results have been obtained with penicillin therapy of late syphilis than of early syphilis. The observed differences between the results of treatment of late and of early syphilis may well be due to the incidence

of reinfections following treatment of early syphilis. In neurosyphilis better results have been obtained with 15- to 20-day periods of therapy than in 8 days. As in the treatment of early syphilis, so in that of late syphilis, slowly absorbed preparations of penicillin need not be given daily when treatment is continued for several weeks. In all probability three or two injections of 450,000 to 600,000 units a week for 4 weeks would give as good results as daily injections of the same amount for 20 days. Until proved otherwise, late latent syphilis and benign forms of symptomatic late syphilis should be treated for at least 15 days with 4,000,000 to 6 000,000 units. Neurosyphilis should be treated for not less than 15 days with 6 000,000 units. A few patients treated for cardiovascular syphilis at Bellevue Hospital have seemed to do well following treatment with only 4 000,000 units of penicillin in 12 days. If well tolerated, however penicillin therapy of cardiovascular syphilis should probably be similar to that given for neurosyphilis.

In the rare case of late syphilis that fails to respond to the doses of penicillin suggested above, arsenicals, bismuth, and, if necessary fever should be tried. I doubt if it is ever wise to continue penicillin therapy of syphilis for more than 6 weeks, and probably not beyond 4 weeks. If strains of T pallidum vary in resistance to penicillin and if some strains increase in resistance during therapy as is true of some strains of streptococci, repeated courses of penicillin with intervening rest periods would be more logical than prolonged continuous treatment. Patients who relapse following penicillin therapy of late syphilis can usually be successfully re-treated with 9,000,000 units of penicillin over a period of 3 to 4 weeks.

REFERENCES

ARNOLD, R. C. MAHONEY J F CUTLER, J C. and LEVITAN S. "Penicillin Therapy in Early Syphilis. III" *J Ven. Dis. Inform.*, 28 241 1947

CHAIN E., and DUTHIE, E. S "Bactericidal and Bacteriolytic Action of Penicillin on the Staphylococcus," *Lancet* 1 652, 1945

CHARGIN L. LEIFER, W and HYMAN H. T "The Application of the Intravenous Drip Method to Chemotherapy as Illustrated by Massive Doses of Arsphenamine in the Treatment of Early Syphilis, *J.A.M.A.*, 104 878 1935

CLARK, W H, BRYNER, S and RANTZ, L. A. "Penicillin-resistant, Nonhemolytic Streptococcus in Subacute Bacterial Endocarditis," *Am. J M d* 4 671 1948.

COMMITTEE ON MEDICAL RESEARCH THE UNITED STATES PUBLIC HEALTH SERVICE "The Treatment of Early Syphilis with Penicillin," *J.A.M.A.*, 131 271 1946

CRAIG R. M. SCHWEMLEIN G X. and KENDELL, H. W "Penicillin Combined with Fever Therapy Preliminary Report of 20 Cases of Early Syphilis," *J Lab & Clin. Med* 30 1016 1945

DATTNER, B. "Treatment of Neurosyphilis with Penicillin Alone at Bellevue Hospital," *Am. J Syph., Gonor & Ven Dis* 32 399 1948.

——— KAUFMAN S S. and THOMAS E. W Penicillin in Treatment of Neurosyphilis," *Arch. Neurol. & Psychiat.*, 58 426 1947

DUNBAR, W B. HAMRE, P M McKEE, C. M. and RAKE, G Action of Penicillin and Other Antibiotics on Treponema Pallidum," *Proc Soc Exper Biol. & Med* 55 158 1944

EAGLE, H. "The Therapeutic Activity of Penicillins F G K, and X against Spirochetes and Streptococci in Vitro " *J Bact.*, 52 81 1946.

——— "The Varying Blood Levels Afforded by Penicillins F G K, and X in Rabbits and Man," *J Exper Med.* 85 175 1947

——— Inactivation of Penicillins F G K, and X by Human and Rabbit Serum," *J Exper Med* 85:141 1947

——— The Treatment of Early and Latent Syphilis in Nine to Twelve Weeks with Triweekly Injections of Mapharsen," *J.A.M.A.*, 126 538, 1944

——— MAGNUSON H. J and FLEISCHMAN R. "The Effect of the Method of Administration on the Therapeutic Efficacy of Sodium Penicillin in Experimental Syphilis," *B ll. Johns H pkins Hosp.*, 79 168, 1946

——— ——— and ——— "The Synergistic Action of Penicillin and Mapharsen (Oxophenarsine Hydrochloride) in the Treatment of Experimental Syphilis, *J Ven. Dis. Inform.* 27 1 1946.

——— ——— and ——— "The Effect of Hyperpyrexia on the Therapeutic Efficacy of Penicillin in Experimental Syphilis," *Am. J Syph., G nor & Ven. Dis.*, 31 239 1947

——— ——— and ——— "Observations on Therapeutic Efficacy in Experimental Syphilis of Calcium Penicillin in Oil and Beeswax and Their Bearing on Its Use in Man," *Am. J Syph., Gonor & Ven. Dis.*, 31 246, 1947

FLEMING W L., and WOLF M. H. "The Therapeutic Effectiveness of Relatively Crude Commercial Penicillin in Early and Late Rabbit Syphilis, *Am. J Syph., Gonor & Ven. Dis.*, 30 468, 1946.

FRAZIER, C. N and FRIEDEN E. H. "Action of Penicillin on Treponema Pallidum, *J.A.M.A* 130 1677 1946.

GOODWIN M S., and MOORE, J E. "Penicillin in Prevention of Prenatal Syphilis, *J.A.M.A.*, 130 688 1946.

HAHN R. D "Late Gummatous Syphilis Resistant to Treatment with Penicillin Case Report," *Am. J Syph Gonor & Ven. Dis.*, 31 542, 1947

HILL, W R Problems Arising in the Treatment of Syphilis with Penicillin, *New England J Med* 235 919 1946.

HOBBY G and DAWSON M. H. "Effect of Rate of Growth of Bacteria on Action of Penicillin," *Proc Soc Exper Biol. & Med* 56 181 1944
—— MEYER, K. and CHAFFEE, E. "Observations on the Mechanism of Action of Penicillin," *Proc Soc Exper Biol. & Med.*, 50 281 1942.
INGRAHAM N R., JR. STOKES, J H. BEERMAN H. LENTZ, J W and WAMMOCK, V S "Penicillin Treatment of the Syphilitic Pregnant Woman," *J.A.M.A.*, 130 683 1946.
"Intensive Arsenotherapy and the Curability of Early Syphilis and Its Applicability as a Criterion of Cure" (editorial) *Am. J Syph. Gonor & Ven. Dis.*, 27 15 1943
LEIFER, W "The Treatment of Early Syphilis with Penicillin," *J.A.M.A.*, 129 1247 1945
LLOYD-JONES T R. ALLEN S. J and DONALDSON E. M. "Out-patient Treatment of Early Syphilis with Penicillin A Survey of 215 Cases Treated by Single Daily Injections," *Brit. M J.*, 1 567 1946.
McDERMOTT W BENOID M. and DUBOIS R. "Time-dose Relationships of Penicillin Therapy Regimens Used in Early Syphilis," *Am. J Syph., Gonor & Ven. Dis.*, 29 345 1945.
McELLIGOTT G L. M. "The Management and Treatment of the Late and Latent Syphilitic," *Brit J Ven. Dis.*, 22 171 1946.
MAGNUSON H. J and EAGLE, H. "The Retardation and Suppression of Experimental Early Syphilis by Small Doses of Penicillin Comparable to Those Used in the Treatment of Gonorrhea," *Am. J Syph Gonor & Ven. Dis.* 29 587 1945.
—— and ROSENAU B. J "Bismuth Plus Penicillin in the Treatment of Experimental Syphilis, *Am J Syph., Gonor & Ven. Dis.*, 32 203 1948.
MAHONEY J F ARNOLD R. C. and HARRIS, A. "Penicillin Treatment of Early Syphilis A Preliminary Report," *Ven. Dis. Inform.*, 24 355 1943
"Mode of Action of Penicillin" (editorial) *Brit. M J.*, 2 464 1945.
MOORE, J E. *Penicillin in Syphilis* Charles C. Thomas, Publisher Springfield, Ill., 1946.
PADGET P "Long-term Results in the Treatment of Early Syphilis," *Am. J Syph Gon & Ven. Dis.*, 24 692, 1940.
PILLSBURY P M. "Penicillin Therapy of Early Syphilis in 14,000 Patients Follow-up Examination of 792 Patients Six or More Months After Treatment," *Am. J Syph. Gonor & Ven. Dis.*, 30 134 1946.
PLATOU R. V HILL, A. J JR. INGRAHAM N R. GOODWIN M. S. WILKINSON E. E. and HANSEN A. E. "Effect of Penicillin in the Treatment of Infantile Congenital Syphilis Further Observations, *Am. J Dis. Child* 72 635 1946
—— —— ET AL. "Early Congenital Syphilis Treatment of Two Hundred and Fifty-two Patients with Penicillin," *J.A.M.A.*, 133:10 1947
RAIZISS G W "The Effect of Penicillin in Experimental Rabbit Syphilis, *Science* 102 329 1945.
RANTZ, L. A., and KIRBY W M. M. "Action of Penicillin on Staphylococcus in Vitro" *J Immunol.*, 48 335 1944

REYNOLDS F W "Treatment Failures Following the Use of Penicillin in Late Syphilis," *Am. J Syph., Gonor & Ven. Dis* 32 253 1948.

SCHOCH A. G and ALEXANDER, L. J "Treatment of Early Syphilis with Penicillin," *J.A.M.A.*, 130 696 1946.

SPEISER, M. FLAUM G MOON ADAMS D and THOMAS E. W Penicillin Therapy for Syphilis in Pregnancy" *J Ven. Dis. Inform.*, 28 108, 1947

STERNBERG, T H., and LEIFER, W "Mapharsen (Oxophenarsine Hydrochloride) Bismuth Treatment of Early Syphilis by 26-week Schedule, *Am. J Syph. Gonor & Ven. Dis.*, 31 1?4 1947

Symposium Under Auspices of Syphilis Study Section, National Institute of Health, *U.S.P.H.S* Apr 1948 Washington, D. C.

THOMAS E. W and WEXLER, G Review of 2,144 Courses of Rapid Treatment for Early Syphilis," *Am. J Syph. Gonor & Ven. Dis.*, 28 529 1944

TODD, E. W "Bacteriolytic Action of Penicillin," *Lancet* 1 74, 1945.

CHAPTER 8

THE EXAMINATION AND EDUCATION OF THE PATIENT

THE diagnosis of syphilis depends on the correlation of information obtained from a careful history a complete physical examination, and pertinent laboratory procedures. Too frequently—and at times erroneously—the diagnosis is based solely on positive STS and little or no attention is paid to history and physical examination. A well-taken history may provide information pointing to the precise time of infection, or on the other hand, it may provide clues indicating that positive STS are of biologic false rather than syphilitic nature. Routine medical histories regarding past illnesses and operations do not yield sufficient data for determining the stage of the syphilitic infection and for deciding the further management of the patient. In every case, we want to know when the infection was acquired if previously diagnosed, when, where, and by what method if previously treated, when where, with what drugs, how much of the drugs, and over what period of time they were given the outcomes of pregnancies the results of blood and spinal-fluid examinations. These are the historical data that help in diagnosing and evaluating a particular case.

In the management of the patient with syphilis it is the duty of the physician to warn the irresponsible patient of the potential dangers of the disease, and to reassure the apprehensive patient so far as possible. Intelligent appraisal of the case is difficult without knowledge of previous treatment and laboratory findings, and every effort should be made to ascertain these facts.

History.—As a rule, printed forms with elaborate history outlines for syphilis are wasteful and burdensome, since of necessity they must include every possible variable of the disease. Nevertheless, at Bellevue Hospital we have used successfully a relatively simple form containing specific questions essential in a syphilis history These are briefly as follows

1 History of early syphilitic lesions. When were they first noted was a diagnosis made if so when, where, and how?

2 History of late manifestations of syphilis. When were they first noted, and when where, and how were they diagnosed?
3 History of results of all pregnancies.
4 History of previous STS. Has the patient ever had previous STS? Where and when were they made, and what were the results?
5 History of previous spinal-fluid examinations. When and where were the tests made and what were the results?
6 History of previous antisyphilitic treatment. When and where was treatment given? What were the amount, kind, and duration of treatment?
7 History of contacts. This should include marital and other contacts. Names need not be mentioned in the record, but it is important to find out if the contacts have been examined, and what the findings were.

Space is also provided for a complete medical history of the patient. A prepared outline such as this facilitates the recording of historical data relevant to syphilis.

The physician must employ tact and perseverance in order to elicit a reliable and complete history from the patient often questions concerning syphilis will be futile, but questions about blood tests and pertinent symptoms will reveal significant data. If the patient has previously visited other clinics or physicians, information should be obtained by writing the clinics or physicians. Once the diagnosis of syphilis is established, the patient should be informed of the fact as tactfully as possible and should be made aware of the implications of the disease.

Physical examination.—It is not within the scope of this book to describe in detail a physical examination, but it should be no less complete for syphilis than for any other systemic disease. When early syphilis is diagnosed by means of dark field examinations or positive STS associated with early lesions, there is an inexcusable temptation to neglect the complete physical examination Often this will result in overlooking minimal *evidences of syphilis and in failure to discover associated diseases of im*portance Only too often patients with sore throat caused by secondary syphilis are treated with topical measures for weeks simply because the physician failed to suspect syphilis, did not completely examine the patient, and took no blood tests for syphilis. In late syphilis, in addition to the usual careful examination of all the systems, ophthalmoscopic examination should be made routinely

The patient with syphilis may also have neoplastic disease, hyperten-

sion, coronary arteriosclerosis, or other disease, and it is only by thorough examination that these are diagnosed. The discovery of associated diseases is important, since they may be more significant than the syphilitic infection. The original physical examination is also of great importance because it serves as a base line to determine improvement or progression of the syphilitic process.

Laboratory procedures.—Every patient with possible early syphilitic lesions should have dark field examinations of serum from the lesions, and blood should be taken for STS. When late syphilis is suspected, in addition to STS a spinal-fluid examination and a fluoroscopic examination of the heart and aorta should be made. In my experience the fluoroscope is more useful in detecting early signs of aortitis than a teleoroentgenogram, but the latter is useful as a permanent record for comparison with later films. A routine urine analysis should be performed in every case. At Bellevue Hospital each syphilis chart calls for the following examinations, all of which must be completed before the final diagnosis is made history physical examination, STS spinal fluid examination fluoroscopic or teleoroentgenographic examination of heart and aorta, urine analysis, and history of contacts.

EDUCATION OF THE PATIENT

The informed patient with syphilis is more likely to follow the instructions of the physician than is the one who has no understanding of the disease. The physician's duty is not fulfilled by making the correct diagnosis and initiating the best modern therapy Time must be devoted to the education of the patient, who, it is hoped, will remain under the physician's care for a period of at least 5 years. In this respect there is an analogy to treatment of cancer for it is only by prolonged observation that permanence of cure can be established.

Because of the social stigma attached to syphilis, apprehensive patients require frequent reassurance. They must understand not only that they are receiving the best possible treatment but also that their case is being handled in the strictest confidence. *All cases of syphilis should be reported* to the local department of health, but in some instances it is better to report the case by number or initials rather than full name. Worry over the social stigma of syphilis, should the diagnosis become known to others, has injured some patients more than the infection.

The physician regards syphilis as a specific infectious disease which is curable by application of appropriate treatment, but, while he considers it a medical problem, he cannot overlook its social implications. The

physician can free himself of the guilt sense attached to venereal disease by society even though he has not yet been able to elevate society to this level. The intelligent physician will convey this attitude to the patient, making him understand that the disease has no more disgraceful significance than pneumonia or measles, or any other infectious disease. This will help to secure the patient's confidence, and, once the latter is obtained, instruction regarding the disease is much easier

The actual treatment of syphilis today is relatively simple, but the management of syphilis does not end with treatment. The patient must continue under observation for a long time after therapy is completed. The necessity of prolonged observation does not mean, as the uninformed individual is inclined to think, that the infection is still present or that the disease can be given to others. The patient must be made aware of the fact that a positive blood test does not necessarily mean active syphilis any more than a positive tuberculin test means active tuberculosis. The practice of treating positive STS when the patient has had adequate therapy is not only medically unsound but also involves misrepresentation to the patient and oftentimes continued anxiety because it implies that a positive test means an active infection.

The physician must explain to the patient that a positive blood test for syphilis does not necessarily indicate the presence of syphilitic germs but of a substance which the body produces as a result of a syphilitic infection Other conditions besides syphilis produce the same or a similar substance which gives positive tests. In the absence of other known causes, however repeatedly positive STS are usually due to either an old or recent syphilitic infection. In early syphilis the blood test usually becomes negative within a relatively short time after therapy In late syphilis the tests may never become negative, or they may do so years after treatment. These facts should be explained as fully as possible. The physician who treats a patient with late syphilis in the expectation of attaining negative STS is misleading the patient, for no amount or kind of treatment may achieve this desideratum much unnecessary anxiety and expense have been caused many individuals because of their belief that persistently positive STS mean an active infection.

Patients must understand that most syphilitic infections can be completely cured, or permanently arrested, with treatment, but that syphilis is an insidious and relapsing disease and that only prolonged posttreatment observation will determine whether or not there is a favorable outcome. Some of the syphilitic germs may have escaped destruction by the therapy and months later they may multiply and produce a recrudes-

cence of the disease. Consequently patients must be observed for years after treatment. Blood tests are essential in determining progress, but even in early syphilis they do not become negative immediately after treatment. In late syphilis they may not become completely negative for 10 years or more after successful therapy. By means of quantitative serologic tests and physical examinations relapses can be detected but as long as the examinations reveal no evidence of relapse (serologic or clinical) there is no need to worry about positive tests. Positive STS in well-treated patients do not mean that the patient is infectious or that the patient should not marry and have children, provided sufficient time has elapsed after therapy to establish reasonably that the infection is arrested.

The physician should assist the well treated patient who still has positive STS and no evidence of active syphilis to retain employment by *certifying that he is not infectious and that he has been well treated.* He should permit such individuals to marry provided the marital partner knows the facts about the case. But all patients should be urged to remain under observation until the tests for syphilis in blood and spinal fluid have been normal for at least 2 years. Patients treated for late syphilis do not require monthly examinations, but they should be examined at about 2-month intervals the first year and less frequently thereafter. Patients treated for early syphilis should be examined every month for 1 year and every 2 or 3 months the second year. The ideal procedure for every patient who has had the disease is to be examined at relatively frequent intervals for the first 2 years after treatment, and at least once a year thereafter for life.

Many individuals who acquire syphilis are indifferent to the dangers inherent in the disease and forget the whole matter as soon as obvious signs and symptoms disappear. Such individuals need to be warned as well as reassured. They must be told that syphilis is a treacherous disease that may smolder in the healthiest body and that by the time serious damage to body structures becomes apparent, it may be too late for treatment to produce a reversal of the symptoms. Unlike most other diseases, syphilis rarely causes pain or other symptoms until serious harm to body structures has occurred, and, therefore, it is impossible to rely on a sense of well-being as an indication that the infection has been checked.

Finally patients must be questioned about contacts and warned of the danger of reinfection. Many patients have been reinfected following rapid treatment of early syphilis by cohabiting with individuals whom they infected and who have not been treated. Because of this danger now

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CHAPTER 9

THE DIAGNOSIS AND TREATMENT OF EARLY INFECTIOUS SYPHILIS

PRIMARY SYPHILIS

THE incubation period and course of primary syphilis were described in Chap. 2. Primary syphilis may be seronegative or seropositive. In the former case the diagnosis is made only by dark field examination, and care must be taken to differentiate between T refringens, T microdentium and macrodentium, and T pallidum.

Chancre.—The older description of a chancre as an indurated sore with a cartilaginous base is an apt description of one type of chancre only Many chancres are not hard, and some are only superficial erosions. Multiple primary lesions on the genitalia are not uncommon, and occasionally especially in women it is difficult to distinguish multiple chancres from secondary syphilitic eroded papules. The safest rule in genital sores is to do tests for syphilis in every case. Careful dark field examinations will reveal T pallida in at least 95 per cent of chancres. When the T pallidum is not found, repeated STS should be made for at least 8 weeks after the sore appeared.

Extragenital chancres occur most frequently on the lips, the nipples, in the throat, and on the fingers. The diagnosis of syphilis in such cases must not be made by inspection but must be established by dark field examinations or repeated STS

The fact that primary lesions have been noted in less than 50 per cent of the women with early syphilis admitted to Bellevue Hospital raises the question whether or not women fail to develop chancres in many cases. Some syphilologists believe that primary lesions occur in women as frequently as in men, but the chancres are not observed. All of the women admitted to our service had careful examinations not only of the external genitalia but of the vagina and cervix. If they had chancres, many of them must have healed before the secondary lesions appeared. I have observed dark-field positive lesions of the vaginal mucosa on only four occasions. In three of these cases there was an associated vaginitis. It

appears that the vaginal mucosa is peculiarly resistant to syphilitic lesions. It is possible that many women are infected with the T pallidum through the vaginal wall but that primary lesions do not develop The suggestion has been made that the acid state of the vaginal mucosa destroys T pallidum, but, so far as I know this has not been proved Certainly treponemes survive without difficulty on the surface of the cervix. The commonest sites of chancres of the female genitalia are the posterior fourchette, the labia, the cervix, and the vaginal introitus.

Regional adenopathy in primary syphilis.—Some enlargement of the regional lymph nodes is present in practically all cases of primary syphilis. Genital chancres are associated with inguinal nodes which are discrete, nontender and usually only moderately enlarged occasionally very large inguinal nodes are present and can be seen as well as palpated. Tender nodes and nodes that suppurate are rarely due to syphilis but usually to some other infection, which may or may not be associated with a chancre. Chancres of the lips or throat are usually accompanied by relatively large satellite buboes which can be seen as well as palpated in the submaxillary submental, or cervical regions.

SECONDARY SYPHILIS

The clinical manifestations of secondary syphilis are diverse and vary greatly in different individuals. They are briefly outlined in the following sections.

Constitutional symptoms.—Malaise and fever are occasionally associated with secondary syphilis, but, in general, systemic symptoms are absent or trivial. Increased erythrocyte sedimentation rates are found in most cases of secondary syphilis. The so-called malignant type of secondary syphilis occurs with extreme rarity and causes such severe illness as to prostrate the patient.

Skin eruptions.—The skin eruptions of secondary syphilis assume various forms, and it is difficult to learn to identify them merely by reading verbal descriptions. The diagnosis of secondary syphilis should not depend solely on the appearance of the skin lesions. The experienced observer can be reasonably certain of the diagnosis, in many cases, from inspection of the lesions alone, but even the expert demands confirmation from laboratory tests. As in the case of genital sores, dark-field examinations and STS should be made in every case where there is the slightest suspicion that an eruption may be syphilitic.

The skin lesions of secondary syphilis may be macular papular or pustular they are never vesicular in acquired syphilis. Bullae may occur

in infants who were infected in utero. Annular lesions superficially resembling ringworm infections are observed almost exclusively in Negroes. Scaly lesions similar to those of psoriasis are occasionally observed in secondary syphilis, and papulopustular lesions may simulate chicken pox and smallpox.

Secondary syphilitic eruptions are usually *bilateral and symmetrical*, but they vary greatly in distribution. The eruption may be generalized, extending from scalp to soles, or the lesions may be limited to localized areas of the skin. I have found only a single papule on the skin of an occasional *patient with secondary syphilis.* The *macular eruption* (*roseola syphilitica*) may be so faint that it is missed entirely and may be noted for the first time when it flares in the Herxheimer reaction following the inception of treatment

T pallida can usually be found by dark-field examination of serum from the papules of secondary syphilis, but they can seldom be demonstrated in macules. The relatively dry lesions of the skin are not infectious by ordinary contact. The most infectious lesions are the moist papules which develop most frequently on the mucous surfaces of the genitalia and anus but also occur where skin surfaces are opposed, e.g., the axillae and submammary folds. When moist papules fuse, they form flat, raised lesions called condylomata lata, which must be differentiated from condylomata acuminata (venereal warts) which are usually wedge-shaped or cauliflowerlike growths. Condylomata lata may occur in the axillae, under the breasts, and between the toes, as well as on the skin and mucous membranes of the genitalia and anus. The boggy skin caused by dermatophytosis (athlete's foot) is an excellent soil for the growth of T pallidum. Most *papules may develop on the feet, especially between the toes, of* patients with dermatophytosis, and they are very infectious.

Mucous-membrane lesions.—In addition to moist papules, erosions of the mucous membranes of the genitalia and anus are frequent in secondary syphilis. Like moist papules, the erosions swarm with T pallida, which are easily found on dark field examination.

Mucous patches which resemble aphthous ulcers (canker sores) may occur on the lips, buccal mucous membranes, tongue, palate, pharynx, and tonsils. Split papules or erosions at the corners of the mouth are not infrequent. *Pharyngitis, which cannot be differentiated in appearance* from the red throat of other infections, is found in about 60 per cent of patients with secondary syphilis. The throat may or may not be sore. Occasionally ulcerative or membranous pharyngitis, simulating Vincent's angina or diphtheria, is caused by secondary syphilis. The syphilitic

etiology of ulcerative pharyngitis has been missed at times when examiners found fusiform bacilli and spirillae in stained smears of throat lesions and, therefore, made a diagnosis of Vincent's angina. Vincent's organisms are commonly found in stomatitis and pharyngitis which are due to other causes, but they are secondary invaders. Secondary syphilis of the throat and mucous membranes of the mouth has often been misdiagnosed this is unfortunate, since the lesions are highly infectious.

Alopecia.—Loss of hair of varying degree may occur in secondary syphilis. Alopecia usually affects the scalp and eyebrows and is irregular and incomplete, producing a moth-eaten appearance. Invariably the hair regrows, since the follicles are not permanently damaged

Ocular involvement.—Iritis or iridocyclitis is the chief ocular manifestation of secondary syphilis. Iritis is usually associated with inflammation of the conjunctivas. Like all secondary lesions, iritis will heal spontaneously but during the inflammation the pupils should be dilated with atropine or homatropine to prevent permanent adhesions of the iris to the lens (posterior synechiae) Occasionally iritis is the only clinical manifestation of a relapse following treatment of early syphilis. In my experience, a relatively high percentage of patients with iritis have had positive spinal fluid findings for syphilis. Neuroretinitis, with edema of the nerve head and patches of exudate in the retina, has been reported in secondary syphilis, but it is of rare occurrence.

Skeletal manifestations.—Secondary syphilis of the bones is usually confined to the periosteum. In severe cases the thickened periosteum can be seen on X-ray examination, but the diagnosis of periostitis is best made by finding patchy areas of tenderness on palpation of the bones. The long bones of the extremities are most frequently involved in very rare instances periostitis of practically all of the bones may occur

I have seen two cases of osteoporosis of the shafts of the long bones in secondary syphilis of several months' duration One of the patients had a malignant type of secondary syphilis, with loss of weight, fever severe pain, and tenderness of all the bones and muscles, ulcerative pharyngitis, amenorrhea, and anemia. X rays revealed several areas of rarefaction beneath the periosteum of the tibias and bones of the forearms. The second case was that of a young woman named as a contact by a man with secondary syphilis. When examined, she was found to have secondary syphilis of at least 4 months duration. She had a slight swelling and marked tenderness of the midportion of the left forearm. X ray revealed a small area of osteoporosis in the shaft of the left ulna (Fig 34) Her pain and swelling disappeared rapidly following treatment with peni-



FIG. 34. Destructive lesion of shaft of left ulna of patient with late secondary syphilis.

cillin, and subsequent X rays showed complete healing of the bone lesion with no evidence of scarring Presumably the bone pathology in this unusual case was due to late secondary syphilis. Healing without any productive changes in the bone occurred rapidly in this case. Late bone lesions do not heal as rapidly and they usually show residual changes.

Myalgias and arthralgias are not unusual in early syphilis. I have rarely if ever seen arthritis which could be definitely attributed to early syphilis, but synovitis with fluid in the joints has been reported. Gonorrhea must be ruled out in all cases of acute arthritis associated with secondary syphilis.

Hepatitis.—Jaundice, with or without enlargement of the liver is one of the infrequent but definite manifestations of secondary syphilis. The diagnosis is confirmed by the response to antisyphilitic treatment. If treatment with arsenical drugs has preceded the hepatitis, further injections of arsenicals are, of course, contraindicated because of the possibility that the hepatitis is due to arsenic. But, in untreated cases of jaundice and secondary syphilis, beginning antisyphilitic therapy with arsenoxide has produced dramatic improvement in patients at Bellevue Hospital. Now that penicillin is available, intensive antisyphilitic treatment can be given without anxiety in all cases of secondary syphilitic hepatitis. Herxheimer reactions may occur but they are not dangerous in early syphilis. Hepatitis, with enlargement of the liver but without icterus, has been reported in secondary syphilis. The etiology of such cases can be determined only by the response to antisyphilitic treatment.

Nephrosis.—Secondary syphilis may cause a transient nephrosis characterized by large amounts of albumin in the urine. The albuminuria may or may not be associated with hematuria. The tubules are the principal kidney structures involved by secondary syphilis, but, when hematuria is present with moderate albuminuria, the urinary picture is more suggestive of glomerulonephritis than nephrosis. A definite diagnosis of secondary syphilis of the kidneys has been made in less than 0.2 per cent of patients with secondary syphilis admitted to Bellevue Hospital. Early syphilis of the kidneys may rarely cause an azotemia of mild degree. The condition is usually discovered by means of routine urine examinations. Rarely edema may be present. There is no evidence that secondary syphilis causes permanent damage to the kidneys. The albuminuria clears dramatically following antisyphilitic treatment. Scott and Clark have reported nephrosis as a result of a Herxheimer reaction in a patient under treatment for secondary syphilis

Secondary syphilis of the central nervous system.—The central nervous system is probably invaded by treponemes in all cases of secondary syphilis, but the reaction of the central-nervous-system tissues to the infection varies greatly in different individuals. Treponemata pallida can be present in the spinal fluid of patients with secondary syphilis without evidence of central-nervous-system inflammation and with normal spinal-fluid tests, as shown by Steiner Wile and Kirchner Chesney and Kemp, Schoenfield and Krey and Geiger In all probability less than 20 per cent of untreated syphilitics develop active late neurosyphilis. As previously stated, untreated syphilitics usually show evidence in the spinal fluid of involvement of the central nervous system during the first 2 years of infection.

In past years most authorities on neurosyphilis (Dattner Lomholt, Neel, Wittgenstein, and others) have stated that pleocytosis is the first evidence of syphilis of the central nervous system. Published reports indicate that the incidence of increased cells in the spinal fluid of patients with secondary syphilis varies from a low of 13 to a high of 33 per cent of cases examined. At Bellevue Hospital we have examined the spinal fluids of over 4,000 patients with secondary syphilis and have found cell counts of more than 4 per cubic millimeter in about 14 per cent, and positive complement fixation tests in only 5 per cent.

Within the past 2 years Maillard, of the New York State Department of Health laboratory examined with special care the spinal fluids of 239 patients admitted to Bellevue Hospital with seropositive primary syphilis and 269 patients with secondary syphilis. He regarded cell counts of 3 or more per cubic millimeter as abnormal. Total protein of more than 30 mgm per cent and colloidal gold tests which added to more than 40 by the new Lange technique were also considered abnormal by Maillard. His normal values for these tests are somewhat lower than those usually accepted. Maillard has had great experience with spinal-fluid tests, and he believes that his normal standards are justified (1) because of the greater incidence of abnormalities in the group with secondary syphilis than in the group with primary syphilis, and (2) because he found that, following successful treatment of early syphilis, spinal-fluid tests which he regarded as abnormal became normal within 3 to 6 months. On the basis of his possibly too rigid criteria, he found spinal-fluid abnormalities as shown in Figs. 35 and 36

From Maillard's studies, the new Lange colloidal gold test appears to be the most sensitive indicator of early syphilitic activity in the central nervous system. With the old Lange colloidal test, few clinicians of ex

FIG. 35. SPINAL-FLUID ABNORMALITIES IN 239 PATIENTS WITH PRIMARY SYPHILIS (MAILLARD)

CELLS OVER 3 PER CUBIC MILLIMETER	TOTAL PROTEIN OVER 30 MGM PER CENT	QUANTITATIVE COLLOIDAL GOLD TESTS OVER 40	POSITIVE COMPLEMENT FIXATION TESTS
5 4%	3 7%	18.4%	0%

FIG 36. SPINAL-FLUID ABNORMALITIES IN 269 PATIENTS WITH SECONDARY SYPHILIS (MAILLARD)

CELLS OVER 5 PER CUBIC MILLIMETER	TOTAL PROTEIN OVER 30 MGM PER CENT	QUANTITATIVE COLLOIDAL GOLD TESTS OVER 40	POSITIVE COMPLEMENT FIXATION TESTS
15.6%	3.3%	42.4%	4.5%

perience would accept slight abnormalities as significant, and the old test was not so sensitive as the new one. It may well be that the new Lange test affords the first evidence of a syphilitic infection of the central nervous system, but, until more is known about the significance of minor abnormalities in the curve than at present, abnormal colloidal gold tests alone cannot be accepted as reliable indication of an early syphilitic inflammation in the central nervous system. Increased cell counts are definite evidence of inflammation, and they are the rule in early neurosyphilis. Very rarely in my experience, have normal cell counts been found in the spinal fluid of untreated patients who had positive spinal fluid complement fixation tests for syphilis. Apart from the colloidal gold tests, Maillard's statistics of spinal-fluid abnormalities in the two groups examined by him are almost identical with those found in a much larger series of patients examined at Bellevue Hospital.

Acute early syphilitic meningitis.—Most early neurosyphilis is asymptomatic. When symptoms occur during the secondary stage, they are caused by acute syphilitic meningitis. Headaches, vertigo, malaise, fever and rarely epileptiform convulsions may be caused by early syphilitic meningitis. In severe cases, stiff neck, positive Kernig's sign, and even coma may be present. Basilar meningitis may injure one or more of the cranial nerves. Involvement of the optic nerve has been reported, causing blurred vision and papillitis. More frequently the third, sixth, seventh, or eighth nerves are injured, causing ptosis of the eyelids, diplopia facial

paralysis, tinnitus, vertigo, and deafness. The signs and symptoms of early syphilitic meningitis usually disappear with effective antisyphilitic treatment. According to Merritt and Moore, untreated cases are likely to develop serious forms of late neurosyphilis.

RELAPSES OF EARLY SYPHILIS

The definition and cause of relapsing early syphilis were discussed in Chaps. . and . During and after unsuccessful antisyphilitic treatment, early syphilis may relapse with the development of new infectious lesions and marked increases in the reagin content of the blood. In some cases the only evidence of relapse is an increase in reagin titers, known as serologic relapse.

The lesions of relapsing early syphilis are similar to those of secondary syphilis, rarely the relapse simulates primary syphilis with the development of a new lesion at the site of the original chancre (monorecidive). Patients who have relapses of early syphilis are infectious, and in most cases T. pallida can be demonstrated in serum from the lesions by dark field examination. The diagnosis of relapsing early syphilis is made by history of previous antisyphilitic treatment, physical examination, dark field examination of serum from lesions, and quantitative STS.

Neurorecurrence.—Relapse of early syphilis in the central nervous system is called neurorecurrence. Originally this term was used to describe relapse of early syphilis with definite neurological signs and symptoms. Stokes broadened the definition to include all relapses of early syphilis associated with spinal-fluid abnormalities. Neurorecurrence frequently manifests itself as an acute meningitis which is often more severe than that observed in patients who had no previous treatment. Owing to the meningitis at the base of the brain, cranial nerve palsies are frequent in neurorecurrence. Complete recovery is the rule in patients who receive prompt and effective antisyphilitic treatment. The diagnosis is confirmed by spinal fluid examination.

TREATMENT OF EARLY SYPHILIS

The advent of penicillin has greatly simplified the treatment of early syphilis and all other forms of the disease. Precautions necessitated by the use of toxic arsenical drugs are a thing of the past. The only contraindication to the use of penicillin is severe sensitization to the antibiotic, which has been rare to date. Serologic and clinical cure are promptly achievable in the majority of cases of early syphilis, and undoubtedly occur in the patients who have small amounts of reagin in the blood 6

months and more after therapy The reader is referred to Chap. 4 for a discussion of the serologic response following treatment of early syphilis. As a rule, the sooner the diagnosis of early syphilis is made and treatment is instituted the sooner do positive STS become negative.

Results of penicillin therapy —At Bellevue Hospital relatively large series of patients with early syphilis have been treated with 10 different schedules of penicillin alone or penicillin combined with other antisyphilitic drugs. The earliest schedules used were (1) 10 000 units of penicillin in aqueous solution every 3 hours for 60 doses, and (2) 40 000 units every 6 hours for 30 doses. The patients treated with these schedules have been under observation for the longest periods, but it is now known that these dosages of penicillin were inadequate, and neither schedule can be recommended. The cumulative failure rate for the series treated with 600 000 units was over 40 per cent by December 31 1947 and over 35 *per cent for the series treated with 1,200 000 units.*

Of the remaining eight schedules, only seven were used sufficiently long ago for evaluation at this time. They called for the following treatments

1. Injections of 20 000 units of amorphous penicillin in aqueous solution every 3 hours for 60 doses plus eight daily injections of 0 04 gm arsenoxide
2. Daily injections of 600 000 units of amorphous penicillin in oil and beeswax for 8 days
3. Injections of 40 000 units of amorphous penicillin in aqueous solution every 3 hours for 60 doses, plus eight daily injections of 0 04 gm arsenoxide and five injections of 0 2 gm bismuth subsalicylate in oil within an 8-day period
4. Injections of 40 000 units of crystalline penicillin G in aqueous solution every 3 hours for 60 doses
5. Injections of 26 666 units of crystalline penicillin G in aqueous solution every 2 hours for 90 doses
6. Injections of 80,000 units of crystalline penicillin G in aqueous solution every 3 hours for 60 doses
7. Injections of 53,333 units of crystalline penicillin G in aqueous solution every 2 hours for 90 doses

To evaluate the results of therapy with these seven different *treatment* schedules, the patients were divided into four diagnostic groups (1) seronegative primary syphilis, (2) seropositive primary syphilis, (3) secondary syphilis, and (4) relapses or reinfections following previous treatment of early syphilis. Patients with serologic or clinical evidence of renewed

activity of the syphilitic infection whether due to relapse or reinfection and patients who had quantitative Kahn tests of 32 or more 9 months after treatment were regarded as failures. The cumulative failure rates for the seven schedules, based on the number of patients kept under observation (not on the total number treated) are summarized in Fig 37

The periods of follow up observations following treatment are not the same for each treatment schedule, but the statistics are based on a follow-up of more than 1 year in all cases. About 63 per cent of the patients in the first three series have been under observation for 2 or more years, and about 70 per cent of the patients in the last four series, treated with crystalline penicillin G have been under observation for more than 1 year The increase in cumulative failure rates with each year of follow-up can be explained by the decreasing number of patients kept under observation and the occasional relapse or reinfection noted after 1 year To compare the last four series treated with penicillin G with the first series treated with 1,200 000 units of amorphous penicillin plus 0.32 gm arsenoxide, it is necessary to know the cumulative failure rate of the penicillin and arsenoxide treated series at a 17-month period of follow-up which would be comparable to that of the four series treated with penicillin G At 17 months, the cumulative failure rates of the series treated with 1,200,000 units of penicillin and 0.32 gm arsenoxide were seronegative primary syphilis, 14 6 per cent seropositive primary syphilis, 20 4 per cent secondary syphilis, 24 4 per cent re treated patients, 18.8 per cent. Of all the relapses or reinfections in the seven series, 51 1 per cent occurred within the first 6 months after treatment, and 80 per cent occurred within the first year after treatment.

The groups treated for seronegative primary syphilis are so small that they are not statistically comparable to the other groups, but it is apparent that the easiest stage of syphilis to cure is primary syphilis before the STS have become positive. From the histories and clinical findings of the so-called failures, it is probable that over 95 per cent of the re-treated patients in the seronegative primary syphilis groups were reinfections, and possibly 50 per cent of those re-treated in the other three groups of each series were reinfections. That more of the patients treated for seronegative primary syphilis were not reinfected may possibly be explained by the observation that patients with primary lesions, who report to clinics promptly before the STS have become positive, usually comprise a more responsible and less promiscuous group than those who report at later periods after infection

The similarity between the failure rates of the groups treated for sero-

SERONEGATIVE PRIMARY

	MONTHS OF FOLLOW-UP	NUMBER TREATED	NUMBER OF OBSERVED FAILURES	CUMULATIVE FAILURE RATE†
1146 patients treated with 1,200,000 units penicillin (20 000 u.q 3 hours for 60 doses) and 0.32 gms Mapharsen, November 1944 to December 1945	36	91	15	20.9
807 patients treated with 600,000 units penicillin in beeswax and oil daily for 8 days, August, 1945 to July 1946	24	62	5	9 0
236 patients treated with 2,400,000 units penicillin (40,000 u.q 3 hours for 60 doses) 0.32 gms Mapharsen, and 5 bismuths, March, 1946, to July 1946	21	20	1	1.3
256 patients treated with 2,400,000 units penicillin G (40 000 u.q 3 hours for 60 doses) July 1946, to June, 1947	17	32	1	3 2
231 patients treated with 2,400,000 units penicillin G (26 666 q 2 hours for 90 doses) July 1946, to June, 1947	17	23	3	18 4
223 patients treated with 4,800,000 units penicillin G (80,000 u.q 3 hours for 60 doses) July 1946, to June, 1947	17	14	0	0
228 patients treated w th 4 800,000 units penicillin G (53 333 q 2 hours for 90 doses) July 1946, t June, 1947	17	14	0	0

* Follow-up through December 1947 † Accumulated failure rate is based on

OF 7 DIFFERENT TREATMENT SCHEDULES OF EARLY SYPHILIS

SEROPOSITIVE PRIMARY			SECONDARY			RE TREATMENTS OF RELAPSES AND REINFECTIONS		
NUMBER TREATED	NUMBER OF OBSERVED FAILURES	CUMULATIVE FAILURE RATE	NUMBER TREATED	NUMBER OF OBSERVED FAILURES	CUMULATIVE FAILURE RATE	NUMBER TREATED	NUMBER OF OBSERVED FAILURES	CUMULATIVE FAILURE RATE
214	38	26.9	743	153	33.1	98	21	38.4
182	25	18.3	455	72	25.0	104	15	19.2
64	5	9 1	137	21	21 4	15	0	0
47	4	9 9	167	18	15.7	10	0	0
60	6	14 7	154	14	18.3	14	1	25.0
26	4	22 3	97	12	18.9	86	12	18 8
37	4	11 4	95	8	12.3	82	8	13 4

the number of patients kept under observation and *not* on the number treated.

positive primary and secondary syphilis and of those re treated because of relapse or reinfection is noteworthy It does not accord with previous observations that secondary syphilis is more difficult to cure than seropositive primary syphilis and that patients treated for relapse are more liable to fail following a second treatment than those treated for an original infection. In my judgment, however the statistics are so vitiated by the occurrence of reinfection that they do not give an accurate picture of the true results of treatment. The incidence of what Schoch has aptly called "ping-pong" reinfection is now admitted by most careful observers to be higher than originally believed. Patients given rapid treatment of early syphilis frequently infected others prior to treatment and were in turn reinfected by those whom they had originally infected Because of this fact, reinfections were more likely to be noted within 2 to 3 months after treatment than later Schoch and Alexander Shaffer and Schamberg and Steiger have published articles on the probable incidence of reinfection following rapid treatment of syphilis, but as yet the only scientific criterion of reinfection is a new primary lesion which develops at a different site from the original one before the quantitative STS have increased from previous levels. Unfortunately relatively few reinfected patients report back to clinics soon enough to fulfill these requirements.

Regardless of the unsolved problem of differentiating between relapse and reinfection, patients who develop new infectious lesions or who have serologic relapse must be re-treated, and about 20 per cent of the observed patients given rapid treatment of early syphilis at Bellevue Hospital with at least 2,400 000 units of penicillin in an 8-day period have had to be re-treated.

As noted in Chap 7 the advent of procaine penicillin G in oil and 2 per cent aluminum monostearate provides opportunities for a greater variety of time-dose relationships in the treatment of syphilis than did previous preparations. Those who treat syphilis will have to keep informed of the reports of results of various schedules of therapy which are now under investigation. A word of caution, however is needed about comparative statistics of different schedules of treatment of early syphilis. The period of follow-up after a given treatment schedule should be at least 1 year and the number of patients actually observed should be over 100. Also, the opportunities for reinfection should be taken into consideration in evaluating results of treatment of early syphilis. Promiscuous patients are more liable to reinfection than nonpromiscuous individuals, and the reservoir of infectious syphilis varies from time to time, even in the same community Because of the above and other variables which enter into

the long-term observation of large groups, statistical analyses do not always give an accurate picture of therapeutic results.

In spite of the past reports of from 15 to 25 per cent re-treatments following penicillin therapy of early syphilis, the available data have proved beyond doubt that penicillin is now the antisyphilitic agent of choice. Arsenical drugs should be reserved for the rare case which fails to respond satisfactorily to penicillin. When re-treatments with penicillin are taken into account, satisfactory results have been obtained in over 95 per cent of the patients treated for early syphilis and observed for 2 or more years at Bellevue Hospital.

Incidence of relapse of early syphilis and seroresistance during or after prolonged treatment with arsenicals and heavy metal compared with that following rapid penicillin therapy.—In 1932, the Cooperative Clinic Group in this country reported on the relapses of early syphilis during and after conventional therapy with arsenicals and heavy metal. Of 167 patients who were given more than 1 year of treatment by the Cooperative Clinics, 9 per cent relapsed or had resistant serologic reactions. Of 620 patients treated irregularly for 1 year or more, 43.5 per cent relapsed or became seroresistant. In view of such statistics, it is difficult to understand why anyone should prefer the old, conventional treatment to that with penicillin which is not only completed more rapidly but is also much safer than the older type of routine treatment.

Obviously if early lesions of syphilis fail to respond to penicillin, arsenoxide and bismuth should be tried, and, if they fail, fever therapy should be given. As yet, however completely resistant lesions of early syphilis to penicillin therapy have not been reported.

SPECIFIC TREATMENT SCHEDULES OF EARLY SYPHILIS

In writing this book I have been more interested in the principles underlying penicillin therapy than in specific schedules of treatment. The physician treating early syphilis now has a fairly wide choice of treatment schedules with penicillin, and he need not conform too rigidly to any one schedule unless he is engaged in research. As treatment with slowly absorbed preparations of penicillin can be given on an ambulatory basis, the use of these preparations will probably be preferred by most physicians. On the basis of available data the minimum treatment schedules of early syphilis with penicillin in oil and wax or procaine penicillin in oil alone are as follows

1 Daily intramuscular injections of 300 000 units for 15 days

2. Daily intramuscular injections of 600 000 units every other day for eight injections

With the new slowly absorbed penicillin salts such as procaine penicillin in oil and 2 per cent aluminum monostearate which has given consistent blood concentrations of more than 0 03 units per cubic centimeter for 4 days after a single injection of 300,000 units, the following treatment schedules should be investigated

1 Intramuscular injections of 600 000 units twice a week for 2 to 3 weeks. (A single weekly injection of 600 000 units for 4 weeks might suffice, but such minimum treatment cannot be advised as yet.)
2 An injection of 1,200 000 to 2 400 000 units once a week for 2 or 3 weeks. This treatment should be equivalent to daily injections of 300 000 units of POB for 15 days.
3 A single treatment with 2 400 000 units intramuscularly is now under investigation but cannot be advised as yet.

The use of aqueous solutions of penicillin is less practical than that of slowly absorbed preparations. If used the minimum schedules of therapy are as follows

1 Injections of 40,000 units every 3 hours for 80 doses
2. Injections of ?00 000 units every 2 hours for 36 doses (Mahoney)

TREATMENT OF RELAPSING EARLY SYPHILIS

At Bellevue Hospital we have not yet observed a patient who failed to respond to penicillin therapy of early syphilis, although a few patients had to be re-treated with penicillin three or four times. It may be that a rare patient will be encountered who requires arsenical drugs and /or fever to obtain cure of early syphilis, but so far we have not found such a case.

Recurrent relapses of early syphilis following penicillin therapy are best described by examples of actual case histories. The pertinent data of two patients who denied the possibility of reinfection though we have no proof that they were not reinfected, are given in Figs. 38 and 39

Both of the patients whose histories are recorded in Figs. 38 and 39 were originally treated with only 600 000 units of penicillin and the first two relapses in each case were re-treated by doubling the dosage of penicillin previously given Obviously such treatment was inadequate in these cases, but when we re treated relapses or reinfections with at least

FIG. 38. CASE ILLUSTRATING RELAPSES OF SECONDARY SYPHILIS WITH THE DEVELOPMENT OF ASYMPTOMATIC NEUROSYPHILIS DURING THE RELAPSE. NORMAL BLOOD AND SPINAL-FLUID TESTS FOLLOWING A THIRD RE-TREATMENT WITH 9,000,000 UNITS OF PENICILLIN

J L., a white female 26 years of age, was admitted to Bellevue Hospital April 15, 1944, with dark-field positive secondary syphilis. She was first treated with 10,000 units of penicillin in aqueous solution every 3 hours for 60 doses. The reports of her quantitative STS t the time of and f llowing treatment ere as follows:

Serologic Tests

DATE	COMP FIX. TITERS	QUANTITATIVE KAHN TESTS	DATE	COMP FIX. TITERS	QUANTITATIVE KAHN TESTS
4/17/44	130	256	5/31/44	12	8
5 3 44	47	64	6 8 44	8	Not done
5 12 44	36	16	6 15 44	12	16
5 18 44	12	8	6 22 44	75	32
5 25 44	9	8	6 29 44	110	128

On June 22, 1944 and June 29 1944 no lesions were found, but spinal fluid examination showed pleocytosis with 81/3 cells and 1 + Wassermann test in .25 cc of spinal fluid. She was re-treated, from July 7 1944, to July 14 1944 ith 40,000 units penicillin in aqueous solution every 6 hours for 30 doses.

Serologic Tests

DATE	COMP FIX. TITERS	QUANTIT TIVE KAHN TESTS	DATE	COMP FIX. TITERS	QUANTIT TIVE KAHN TESTS
7/ 7/44	160	128	10/ 5/44	N t done	128
8 10 44	36	32	10 23 44	Not done	256
9 7 44	36	16	10 24 44	120	Not done

N lesions were found at the time of her second serologic relapse. The spinal-fluid complement fixation titer was 15; cells, 160/3 total protein, 26 colloidal gold test added to 94 She was re-treated from October 23 1944 to October 30, 1944 with 40,000 units penicillin in aqueous solution every 3 hours for 60 doses and 0.3 gm mapharsen (5 × .06)

Serologic Tests

DATE	COMP FIX. TITERS	QUANTIT TIVE KAHN TESTS	DATE	COMP FIX. TITERS	QUANTIT TIVE KAHN TESTS
10/23/44	120	256	1/ 4/45	Not done	16
11 22 44	Not done	32	1 11 45	N t done	8
11 30 44	Not done	32	1 28 45	Not done	16
12 7 44	Not done	16	2 1 45	Not done	32
12 14 44	Not done	16	2 15 45	96	128
12 21 44	Not done	8			

On March 5, 1945 singl dark-field positive papule was found on the right labium major, and solitary papules were found on the left forearm and back, respectively Her spinal-fluid tests on March 6, 1945 were Wassermann, negative; cells, 173/3 total protein, 27 colloidal gold not done. She was re-treated from March 15 1945 to March 20, 1945 with 50,000 units penicillin in aqueous solution every 2 hours for 180 doses—total 9,000,000 units.

2,400 000 units of penicillin in 8 days, about 80 per cent had satisfactory results. Genuine relapses of early syphilis should be re-treated for a longer period than 8 days. The minimum schedule of re-treatment that I would suggest at present is daily injections of 300 000 units of POB or procaine penicillin in oil alone for 16 days. Other possible treatment schedules are injections of 600 000 units of procaine penicillin in oil and aluminum monostearate twice a week for 4 to 6 weeks. For second relapses a minimum of 9 000 000 units of penicillin should be given over a period of 4 to 6 weeks, and, if desired, the course of penicillin can be followed by arsenoxide and bismuth therapy as suggested in Chap. 7

ADDENDUM

Since this chapter was written the extended period of follow-up on patients treated for early syphilis with 600 000 units of POB daily for 15 days has revealed unusually successful results. Of 134 patients observed for 6 to 12 months, 3 were re-treated because of reinfections, all having had new chancres at different sites from the original ones, and 2 still have *Kahn titers of 32 more than 6 months after treatment. This series is not* comparable with the earlier treated series because of the marked decrease in the reservoir of infectious syphilis and because of the opportunities for more thorough preventive measures against reinfection Nevertheless, it is possible that some strains of treponemes require more prolonged therapy than do others. It is also possible that some strains require higher blood concentrations of penicillin than are permitted by the very slowly absorbed preparations containing aluminum monostearate.

The Central Statistical Unit of the Subcommittee for Venereal Diseases of the National Institute of Health has reported no significant difference between 8- and 15-day treatment schedules when 20,000 to 40 000 units of penicillin in aqueous solution were given every 3 hours. The Committee is now investigating the following 3 new schedules of therapy for early syphilis using procaine penicillin G in oil and aluminum monostearate

1. 1 200 000 units in a single injection
2. 1,200 000 units once a week for 2 weeks
3. 1 200 000 units once a week for 4 weeks.

The evaluation of these treatment schedules *is of great importance, but* it will require at least a year before conclusions can be made as to their value. So far the best results at Bellevue Hospital have been obtained with daily injections of 600 000 units of POB for 15 days.

REFERENCES *

ARNOLD, R. C. MAHONEY J F and CUTLER, J C. Reinfection in E perimental Syphilis in Rabbits Following Penicillin Therapy *Am. J Syph., Gonor & Ven. Dis.* 31 264 1947

"Changing Concept of Reinfection with Syphilis and Its Applicability as a Criterion of Cure, The," *Am. J Syph. Gonor & Ven. Dis* 29 474 1945.

CHESNEY A. M., and KEMP J E. "Incidence of Spirochaeta Pallida in Cerebrospinal Fluid During Early Stage of Syphilis," *J.A.M.A.* 83 1725 1924

CLARK, E. G MAXWELL, R. W and SCOTT V "The Serologic Response Following Penicillin Therapy for Early Syphilis," *Am. J M Sc.,* 213 535 1947

COOPERATIVE CLINICAL GROUP "Cooperative Clinical Studies in the Treat ment of Syphilis. III Results of Treatment in Early Syphilis," *J Ven. Dis. Inform.,* 13 253 1932.

GEIGER, L. R. "Uber den Nachweis und das Vorkommen von Spirochaeten im Liquor bei Frühluetikern," *Arch f Dermat l.,* 162 473 1931

GLASER, R. J and SCOTT V "Destructive Osseous Lesions in Early Syphilis, Response Following Penicillin Therapy Case Report," *Am. J Med.* 3 496 1947

HELLER, J R., JR. BOWMAN R. W PRICE, E. V "Rapid Treatment of Early Syphilis Progress Report, December 1947 *J Ven. Dis Inf rm.,* 29 103 1948.

KAMPMEIER, R. H. *Essentials f Syphilology* J B. Lippincott Company Philadelphia, 1943

LOMHOLT E. *C u se f Chang s in the Spinal Fluid f Syphilitics* Levin & Munksgaard, Copenhagen, 1936

NEEL, A. V *The C ntent of Cells and P oteins in the Normal Cer brospinal Fluid The Diagnostic Importance f Demonst ating Small Pathologic Changes in the Cells and Proteins The Technique of th Invest gation,* Munksgaard, Copenhagen 1939

Recent Advanc in th Study f Venereal Diseases A Sympos m, published by the Venereal Disease Education Institut in co-operation with the United States Public Health Service, Washington, D C 1948.

SCHAMBERG, I L., and STEIGER, H. P "Syphilitic Relapse vs. Reinfection, *J Ven. Dis. Inform* 29 91 1948.

SCHOCH A. G., and ALEXANDER, L J Reinfection in Syphilis Newer Concept of Reinfection Encountered w th Ten-day Arsenotherapy of Early Syphilis Contr lled by Quantitative Serologic Tests, *Am J Syph., Gonor & Ven. Dis.,* 30 173 1946.

——— and ——— Reinfection and Relapse, Analysis of 137 Cases of In-

* A complete bibliography of articles on penicillin therapy of earl syphilis is not given The reade is advised to keep informed of the curren literature.

—fection Failure Occurring in a Total Series of 1 105 Cases of Early Syphilis Treated with Penicillin" *Arch. Dermat. & Syph.* (in press)

SCHÖNFELD, W and KREY L "Das Vorkommen von Spirochaeten im Liquor von Syphilitikern und deren Beziehung zu anderen Liquorbefunden," *München. med Wchnschr.*, 74 413 1927

SCOTT V., and CLARK, E. G "Syphilitic Nephrosis as Manifestation of Renal Herxheimer Reaction Following Penicillin Therapy for Early Syphilis, Case Report," *Am J Syph Gonor & Ven. Dis.*, 30 463 1946.

SHAFFER, L. W "Criteria of Reinfection in Syphilis," *Ven. Dis. Inf rm.*, 24 113 1943

STOKES J H. BEERMAN H. and INGRAHAM N R., JR. *Modern Clinical Syphilology* 3rd ed W B. Saunders Company Philadelphia 1944

THOMAS E. W and WEXLER, G "Review of 2 144 Courses of Rapid Treatment for Early Syphilis," *Am. J Syph., Gonor & Ven. Dis* 28 529 1944

——— and SCHUR, M "Clinical Nephropathies in Early Syphilis, *Arch. Int Med* 78 679 1946.

WILE, U J and KIRCHNER, A. "New Method for Demonstration of Spirochaeta pallida in Spinal Fluid" *Arch. Dermat & Syph* 8 831 1923.

WITTGENSTEIN A "Die Prognostische Bedeutung des Liquorbefundes bei Seronegativen Patienten der Spätlatenz," *Ztschr f d. ges. Phys. Therap* 35 224 1928.

CHAPTER 10

LATENT SYPHILIS

Since latent syphilis is asymptomatic, the diagnosis can only be made by means of history and positive STS. Judging from histories obtained at Bellevue Hospital, many individuals having positive STS will not admit any knowledge of signs or symptoms of early syphilis. As a result, very frequently latent syphilis has to be diagnosed solely on the basis of positive serologic tests. However not every individual with positive STS has syphilis, and patients have undoubtedly been treated for the disease when it was not present. I know of no way to avoid this mistake in every case. In the absence of any known cause of biologic false positive reactions, untreated individuals who have repeatedly positive STS presumably have or have had syphilis. The degree of activity of the infection during latency is unknown, and we have no way of predicting the probable outcome in a given case. Consequently in the management of the individual case of latent syphilis, the physician treats in order to prevent progression of the disease even though it may never occur To admit this fact does not mean that the diagnosis of latent syphilis cannot usually be justified, or that we have no knowledge as to the kind and amount of treatment which should be given to protect the patient. The knowledge at our disposal, however cannot foretell the eventual course of a given case we know that many untreated individuals with no other evidence of syphilis than positive STS suffer no demonstrable damage from the disease, while others ultimately develop serious manifestations. Our knowledge of latent syphilis depends on the study of large numbers of patients and on the recorded observations of careful and experienced observers of syphilis. From these sources we know fairly well what to expect of untreated latent syphilis in the mass but not in the individual. It has been estimated that about 25 per cent of individuals with untreated latent syphilis subsequently develop demonstrable signs of the disease.

DIAGNOSIS

Latent syphilis is not an emergency and the diagnosis should not be

made hastily A carefully taken history may or may not assist in confirming the diagnosis. In the absence of a definite history of syphilis, repeated STS are necessary for diagnosis, and the spinal fluid must always be examined to rule out asymptomatic neurosyphilis. In addition, cardiovascular syphilis should be excluded by X-ray examination of the aorta and heart. When possible, the sexual contacts of patients with positive STS should be studied. If the contacts show no evidence of syphilis and the patient's history and physical examination afford no clue to the probability of infection, syphilis is still a possibility unless a definite diagnosis of biologic false positive reactions can be made. Criteria for the latter diagnosis were given in the sections on that topic in Chap. 4 The failure to meet the requirements of a diagnosis of biologic false positive reactions does not necessarily establish the presence of syphilis, but it is perhaps advisable to treat such patients as a precautionary measure. However in all doubtful cases that have a negative history for syphilis, a diagnosis of possible syphilis is more exact than one of actual syphilis, and the patient should be so informed.

Difficulties encountered by patients with latent syphilis.—The first difficulty encountered by individuals with latent syphilis is the fact that, unless they themselves suspect the infection or undergo routine STS, the disease will not be discovered. In some cases the diagnosis is not made in the latent phase and awaits the appearance of definite signs and symptoms of late syphilis. Therefore, the practice of taking routine STS on patients is commendable, even though at times it leads to much suffering on the part of individuals who are not infectious to others, as proved by the examination of their sexual contacts and even though they are in good health, some develop anxiety neuroses because of the presence of a substance in their blood the significance of which is not yet fully known. Part of the management of such cases is to help the patients to keep their jobs and to relieve them of unnecessary worry

Unless properly informed about positive STS the patient with latent syphilis is inclined to attribute every ache and pain and blemish of the skin to the disease. And unless properly informed, the physician easily falls into the same error Positive STS offer a convenient diagnostic common denominator for all the ills of man, with the result that other possible causes of a patient's complaints are often overlooked. For example, repeated miscarriages in a woman with positive STS are not necessarily due to syphilis. It is easy to attribute them to syphilis and to continue antisyphilitic treatment indefinitely in the hope of correcting a condition which may not be due to syphilis, especially if the miscarriages continue

after the patient has received even moderate amounts of antisyphilitic treatment. Neurologic complaints of patients with positive blood tests and negative spinal-fluid tests for syphilis are rarely if ever due to active neurosyphilis, yet it is often easier to continue antisyphilitic treatment than to seek the real cause of the trouble. The index of suspicion regarding syphilis should be kept at a high level, but so too should be the knowledge of the disease. It is futile to keep treating late syphilis, far beyond the adequate therapeutic point, in the hope of reversing the STS to negative and of clearing up symptoms that may have no relation to the disease.

PROGNOSIS

It was pointed out previously that about one of four individuals with untreated latent syphilis develops definite late symptoms and signs of the infection. But there is no longer reason to believe that latent syphilis requires the amount and duration of treatment that was formerly advised. It is now recognized that very few individuals, given regular treatment of latent syphilis with as many as 20 injections of arsenicals and 20 of bismuth, have subsequently developed demonstrable late syphilitic lesions. I cannot recall any patient treated continuously for latent syphilis with alternate courses of arsenical drugs and bismuth for 1 year who later showed evidence of progression of the disease. There may be exceptions to this rule, but such rare exceptions do not establish criteria of adequate treatment. Patients with arrested tuberculosis are not kept at rest indefinitely because a few will relapse. They are, however, cautioned to remain under medical observation, and the same advice applies to patients who have had adequate treatment of latent syphilis.

According to the reports of the Cooperative Clinic Group, positive STS were reversed to negative in about one-third of patients treated for latent syphilis with the older forms of conventional therapy. This estimate probably includes some individuals who were treated for early latent syphilis of less than 2 years duration. In my experience, reversal of positive STS to negative cannot be expected in one-third of patients treated for late latent syphilis—at least not within 5 years after treatment. It is true, however, that the longer the period of observation after therapy, the higher is the percentage of patients who become seronegative. Moore has stated that 6 months of treatment with arsenical drugs and heavy metal will protect 95 to 98 per cent of patients with latent syphilis. Although I have inadequate statistical data to support this statement, I have no reason to question the accuracy of Moore's conclusion.

AGE 35

B.W.R.
END POINT
TITRATIONS

22 ARSENICALS
23 BISMUTH

THERAPY

DATE

First Knowledge

FIG 41 Chart showing serologic response of a patient who eceived irregular treat ment for latent syphili from July 1933 to January 1937 When first seen in prison he had complement fixation titers of more than 35 units. During th f llowing 3 years, without further treatment, the titers fell to relatively low levels and then showed minor fluctuations.

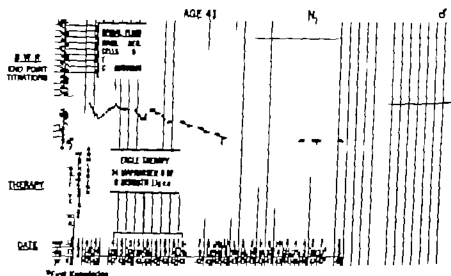


FIG. 42 Chart showing the serologic response of patient with latent syphili treated in prison by the Eagle method of intensi e arsenotherapy

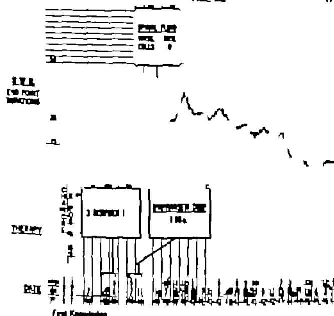


FIG. 43. Chart showing the serologic response following treatment of latent syphilis with massive arsenotherapy given by intravenous drip.

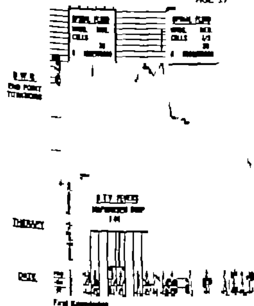


FIG. 44. Chart showing the serologi response following combined fever and massive arsenotherapy gi en by int avenous drip. Not that there is no drop in titers for 1 ear following tre tment after which time the titers f ll sharply

AGE 21 N. ♂

FIG 45. Chart showing the serologic response f llowing treatment of latent syphilis with penicillin.

AGE 19 N. ♂

FIG 46. Chart showing 10-year follow-up of patient who had relatively small amounts of treatment in 1936 nd 1938. There is no reason t believe that re treatment of this patient would have altered the serologic course in any way

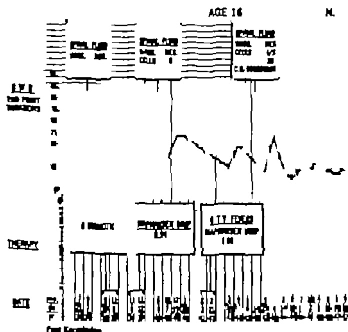


FIG. 47 Chart showing the failure of re-treatment with metals and fever to lower the reagin titers of a patient previously treated for latent syphilis.

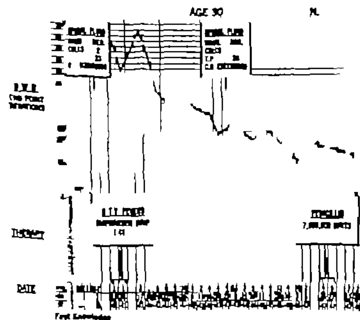


FIG. 48. Chart showing the failure of re-treatment with penicillin t influence the reagin titers in patient who had had adequate previous therapy After large amounts of penicillin the STS titers remained about the same for 10 months.

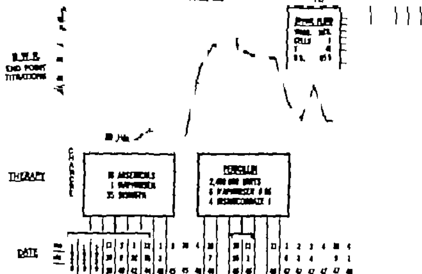


FIG 49 Chart showing a serologic relapse which occurred 1 year after the original treatment of a patient with latent syphilis of 18 years' duration. Note that the marked increase in titers following the relapse persisted for 6 months before re treatment was started, and that there was a sharp drop in titers after re-treatment.

FIG. 50. Chart showing probable reinfection of a patient who wa treated for early latent syphilis in 1942. Whil on probation from prison 4 years later when the STS titers were at a low level, he ga·e a history of exposure and penil ledons followed by a marked rise in titer.

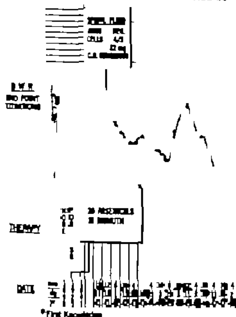


FIG. 51. Chart showing fluctuations of low STS titer following treatment with more than 20 arsenicals and 20 bismuth injections.

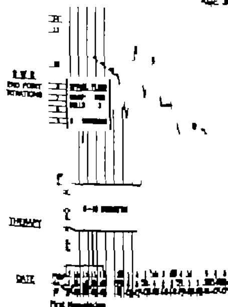


FIG. 52. Chart showing fluctuations of low STS titer following a very small amount of treatment with bismuth alone.

Figures 51 and 52 show spontaneous, unexplained fluctuations in titers following treatment of patients with relatively small amounts of reagin in the serum.

PENICILLIN TREATMENT SCHEDULE FOR LATENT SYPHILIS

Any of the schedules suggested for secondary syphilis would probably suffice for the treatment of latent syphilis. A minimum of 4 000 000 units of penicillin in not less than 12 days is advised. The evidence accumulated by Kaplan on large series of patients with latent syphilis should convince the most skeptical of the futility of continuing treatment of latent syphilis in the hope of hastening the reversal of positive STS to negative. Re treatment of asymptomatic patients who have had reasonably good previous therapy is indicated only in cases showing definite serologic relapse or reinfection.

REFERENCES

Diekker, T H Clark E. G and Moore, J E. "Long Term Results in the Treatment of Latent Syphilis," *Am. J Syph. Gonor & Ven Dis* 28 1 1944

Jordon J W and Dolce, F A. Latent Syphilis Study of One Hundred and Sixty nine Cases Observed Ten Years or More," *Arch Dermat & Syph* 54 1 1946.

Kaplan B. I and Brightman I J "Studies on Therapeutic Procedures in Latent and Late Syphilis," *Am. J Syph. Gonor & Ven Dis.*, 28 192 1944

McElligott G L. M "The Management and Treatment of the Late and Latent Syphilitic," *Brit J Ven. Dis.* 22 171 1946.

Moore, J E. "Seroresistance (Wassermann Fastness) A Discussion for the Patients," *Am. J Syph. Gonor & Ven. Dis.*, 30 125 1946.

CHAPTER 11

LATE BENIGN SYPHILIS

IN Chap. 2 it was pointed out that the early manifestations of syphilis are those of a self-limited, acute infection. Late symptomatic syphilis, on the other hand, exhibits most of the possible manifestations of chronic infections and degenerative conditions. To fully understand the biologic changes that take place in the acute and chronic stages of the disease, we would have to know much more than we now do about obscure problems in microbiology, immunology, and physiology. Some of these problems were presented in earlier chapters, and the sections which follow should be read in the light of previous discussion.

The late manifestations of syphilis include an almost overwhelming multiplicity of variables. To explore thoroughly all possible differential diagnoses for every sign and symptom of late syphilis would require a very large textbook, comprising medical and surgical aspects, and features involving most of the specialties. This monograph is not intended to be such a monumental work, and I do not believe that such a tome would help the clinician to diagnose syphilis, however valuable it might be otherwise. A careful history and physical examination and a comprehensive knowledge of other diseases are of great importance in the management of syphilis, but a high index of suspicion will reward the physician with a correct diagnosis of syphilis in most cases. Laboratory tests are as essential for the diagnosis of late as of early syphilis, but in late syphilis, unlike early syphilis, the diagnosis of lesions, apart from those in the central nervous and cardiovascular systems, must at times depend on a therapeutic test. Syphilis has an inexhaustible ability to surprise even experienced observers, and descriptions of its unusual manifestations are of value primarily in raising the index of suspicion. Failure to make necessary blood and spinal fluid tests has frequently led to failure to diagnose the disease, but it must be remembered that the complaints and abnormal physical findings of patients with positive serologic tests for syphilis are not necessarily caused by the specific infection. Occasionally it may be necessary to procure presumptive proof of the syphilitic etiology of a given lesion by a therapeutic test. When penicillin is used for the test,

healing of the lesions does not conclusively prove their syphilitic etiology since penicillin is effective against many other infections. Nevertheless, from the point of view of patient and physician, penicillin is the agent of choice because it is the most effective and least dangerous drug Symptoms and signs that fail to respond to penicillin therapy are usually not syphilitic in origin but when the probability of syphilitic etiology is great and penicillin fails, other forms of antisyphilitic treatment may be tried. However it is fortunate that the infection can usually be diagnosed correctly and readily by history and laboratory tests. In the following sections the late manifestations of syphilis are classified and described briefly and the effect of treatment on the lesions is presented.

INCIDENCE OF SO-CALLED BENIGN LATE SYPHILITIC LESIONS

The incidence of demonstrable late syphilitic lesions of the skin mucous membranes, skeletal system, and viscera of patients observed at Bellevue Hospital has definitely declined in the past decade. This is probably due to improvement in case finding and treatment during the past ?0 years. I doubt that statistics of the incidence of the so-called benign late lesions of syphilis have much significance at present. The incidence undoubtedly varies in different communities. In Bruusgaard's report of 473 untreated patients, the incidence of late lesions of the skin, mucosae, and bones was 12.2 per cent.

LATE SYPHILIS OF THE SKIN

Late cutaneous syphilides may develop at any time after the secondary stage. Precocious tertiary lesions of the skin may be noted within the first year or two of the infection, and it is not unusual for late syphilides to develop 20 or 30 years after infection.

Precocious tertiary syphilides.—With conventional antisyphilitic therapy of former years, precocious tertiary lesions with borderline characteristics between secondary and late cutaneous lesions were not rare during the first 4 years after infection They were observed more frequently in inadequately treated than in untreated patients. Treponema pallidum can rarely be demonstrated in precocious tertiarism by dark field examination, and, as a rule, the lesions heal with little or no scarring The eruptions consist of papules which are suggestive of the nodules of late syphilides and usually some degree of ulceration is present. The eruption may be generalized or localized but the papules usually occur in circumscribed groups.

Late syphilides.—The cutaneous manifestations of late syphilis consist of (1) gumma, and (2) tertiary eruptions of grouped nodules which may or may not ulcerate. The grouped eruptions usually but not always form segments of circles.

Gumma.—A gumma of the skin begins as a small or large tumor which breaks down, forming an ulcer which, in most cases, is indistinguishable from other chronic ulcers. Biopsies do not always help in the diagnosis because the pathologic picture may be that of a nonspecific, chronic inflammatory process. When the biopsy presents a histologic picture characteristic of syphilis, the diagnosis is usually definite however if the lesion fails to respond to satisfactory antisyphilitic treatment, the clinician will have to consider other specific granulomas. Syphilis should be ruled out in every case of chronic ulcer The STS are almost always positive in patients with gummas, but I have observed a single instance of complete seronegativity in a patient with an ulcer of several months duration which healed promptly with arsenotherapy When the diagnosis seems justifiable on clinical grounds and the STS are negative, a therapeutic test is in order Cutaneous gummas may be single or multiple and may occur anywhere on the surface of the body The ulcers may heal spontaneously but generally new lesions develop in adjacent areas. The scars of gummas are thin and soft, but they cannot be differentiated from those of certain burns and other injuries. The marked disfiguration with destruction of the nose, and the ulceration and scarring of the forehead and face, described in the older textbooks on syphilis, are rarely seen today I observed one such case in 1938 that had been diagnosed as an X-ray burn and treated accordingly for years without a serologic test for syphilis ever having been made.

Pseudochancre redux is a term used to describe solitary gumma of the penis, which must be differentiated from a primary lesion.

Nodular and nodulo-ulcerative lesions.—The grouped skin syphilides usually have a characteristic appearance which is readily recognized by experienced observers. However in every case the diagnosis should be confirmed by serologic testing and further corroborated by satisfactory response to antisyphilitic treatment. The characteristic polycyclic or arcuate configuration is not always present in these lesions.

LATE SYPHILIS OF THE MOUTH, TONGUE, AND THROAT

The late syphilitic lesions of the mouth, tongue, and throat may be nodular or ulcerative or they may consist of infiltrated areas of chronic

inflammation The most common lesion is gumma of the soft or hard palate. Perforations of the palate remain after healing has taken place. Syphilitic sore throat is much more common in the secondary than the late stage of infection. Late lesions of the pharynx, tonsils, and pillars of the fauces are easily misdiagnosed. They may consist of a solitary gumma of nodules, or of diffuse ulcerative inflammation covered by a grayish slough. The most common late lesion of the tongue is a gumma usually located on the dorsal aspect, and this must be differentiated from carcinoma. Diffuse syphilitic glossitis has been described and must be differentiated from leukoplakia and lichen planus, and other forms of sclerosing glossitis. Differential diagnosis in such cases may be difficult, and the diagnosis of syphilis is generally based on collateral clinical and laboratory data. Gummas or nodular lesions of the lips and buccal mucous membranes are rare.

Leukoplakia, which manifests itself as white patches on the tongue or buccal mucous membranes, and on the lips, is due less often to syphilis than was formerly believed. In most cases leukoplakia is due to chronic irritation from smoking jagged teeth, and low-grade infection. It occurs more frequently in syphilitics than in nonsyphilitics. Malignant metaplasia may take place in leukoplakia, but many patients have the condition for years without degenerative changes.

LATE SYPHILIS OF THE EYE

Iritis.—Late syphilis may rarely cause an iritis similar to that seen in secondary syphilis except that the inflammation of the iris is more chronic there may be associated infiltration of the cornea, constituting a keratoiritis. The condition usually responds rapidly to antisyphilitic therapy and the cloudiness of the cornea rarely persists for months, as is usual in the interstitial keratitis of congenital syphilis.

Chorioretinitis.—Gummatous infiltration of the choroid is not unusual in late syphilis. Oftentimes the condition is practically symptomless, and the diagnosis is made only by routine examination of the fundi with the ophthalmoscope When the lesions occur in the area of the macula, the vision is seriously impaired. On visualizing the fundus of the eye, areas of white exudate may be seen in active chorioretinitis healed lesions show white patches of sclera surrounded by black pigment where the choroid and retina have been destroyed. Syphilis is not the only cause of chorioretinitis, and there is nothing specific about the appearance of the choroidal lesions due to syphilis. An active chorioretinitis in a known syphilitic should receive the benefit of antisyphilitic treatment, unless

some other etiology can be definitely established. Most instances of chorioretinitis in patients who have had antisyphilitic treatment are actually healed, and the ophthalmoscopic examination reveals the residua of previous active foci.

Interstitial keratitis.—Interstitial keratitis is one of the unexplained phenomena of syphilis. I have seen it only in patients who had congenital syphilis, but Stokes and others state that it may rarely develop in late acquired syphilis. The lesion consists of a vascularization of the cornea, with blood vessels running between the corneal layers. The vascularization is associated with keratitic precipitates consisting of cells and pigment which form on the posterior surface of the cornea. The cornea becomes cloudy and, on examination with the slit lamp the blood vessels can be seen in the interstitium. Occasionally patients are seen who can hardly see light through the marked opacities of the cornea.

In my experience, the most usual time for interstitial keratitis to develop in congenital syphilitics is between the ages of 10 and 20 but it may occur any time after 2 years of age. We recently had a patient who first developed interstitial keratitis at the age of 31 he had had a small amount of antisyphilitic treatment at 6 years of age, and he denied any serious illnesses or complaints up to the time when the keratitis started. He had no evidence of syphilis on physical examination except the keratitis and positive STS.

The vascularization of the cornea may begin simultaneously in both eyes It may start in one eye and later develop in the other or it may be confined to one eye. Several of our patients with congenital syphilis developed interstitial keratitis after malaria therapy for neurosyphilis. The precipitating cause of the condition is unknown. The duration of the keratitis varies greatly depending in part on the degree of vascularization and apparently on other unknown factors. In most cases the disease seems to run its course in from 12 to 18 months, regardless of the type of antisyphilitic treatment given. After healing has occurred, the empty blood vessels remain in the interstitium for long periods, and occasionally a few small, opaque patches may persist permanently

Why congenital syphilitics so frequently develop interstitial keratitis is unknown. Obviously in such cases there must be developmental changes which make the corneas especially liable to vascularization. Klauder who has made one of the most thorough studies of the subject, has reached no definite conclusions regarding its pathogenesis.

Treatment—Most ophthalmologists agree that it is extraordinarily difficult to evaluate the effects of antisyphilitic treatment in cases of inter

stitial keratitis. At Bellevue Hospital we have used every type of therapy including mercury inunctions, arsenicals, bismuth, fever therapy and penicillin, without having reached any definite conclusions as to their relative effectiveness. In some cases the corneal opacities cleared fairly rapidly while in others, that were given much more therapy the keratitis persisted for many months with very gradual healing Both penicillin and fever therapy are preferred to heavy metal, but I have not found that fever seemed to hasten the very gradual improvement in several patients who had received previous therapy with penicillin Klauder cautiously states that fever therapy appears to be the most effective form of treatment." * He believes that penicillin can replace metal chemotherapy and he advises penicillin plus fever therapy

LATE SYPHILIS OF THE MUSCLES AND FASCIA

Myositis and fibrositis have been attributed to late syphilis. The diagnosis is difficult to make with accuracy I have rarely had occasion to suspect the presence of syphilitic myositis or fibrositis, but patients on a few occasions have reported relief of muscle pains following therapy Muscle biopsies in such cases were not done, but it might be of value to do them, as small granulomas have been reported in the muscles of patients with rheumatoid arthritis and other conditions. Similar lesions might be found in syphilitic patients with muscle pain.

LATE SYPHILIS OF THE BONES

According to Stokes, "clinical experience suggests that few syphilitic patients indeed manage to escape some degree of reaction in this group of structures [skeletal system] at some time in the course of their infection. The proportion of clinically detectable syphilis of the bones will, of course vary with the stage of the disease and the thoroughness of the examination." † It is true that occasionally patients state that they have been relieved of pain in bones during antisyphilitic treatment, even though X ray examination failed to reveal pathology of the bones. The expense of taking roentgenograms of all the bones of every patient with late syphilis is prohibitive, and it may be that bone syphilis is missed in some cases, but, in my experience, demonstrable evidence of late lesions in the bones is found in a relatively low percentage of adult syphilitics. From a practical point of view X ray examinations of the bones are rarely

* Klauder, J V "Treatment of Interstitial Keratitis with Particular Reference to Results of Penicillin Therapy *Am. J Syph. Gon & Ven Dis.*, 31 569 1947

† Stokes J H Beerman H and Ingraham N R *Modern Clinical Syphilology* 3rd ed W B Saunders Company Philadelphia, 1944 p. 765

helpful unless pain, swelling, or other evidence of bone disease is present. In some cases marked proliferation of bone occurs without the patient being aware of the process. Whether or not the pathologic process causes pain or disability antisyphilitic treatment will usually stop further progress of the disease and prevent symptoms.

Gumma.—A gumma of the bone is always destructive and causes a localized area of osteoporosis which must be differentiated chiefly from osteosarcoma and tuberculosis. The tissues surrounding a bone gumma are frequently swollen, and sinuses may develop Bone gummas usually occur at the diaphyses of the long bones and very rarely develop in the shaft. A favorite site of bone gumma is the sternal end of the clavicle, with involvement of the sternoclavicular joint and swelling of the surrounding soft tissues.

Diffuse osteitis of late syphilis is usually a low-grade inflammation which is preponderantly osteoplastic, or productive of bone. It is usually but not always associated with demonstrable periostitis. At times, areas of marked osteoporosis are noted in association with increased density of other parts of the bone. The tibias and fibulas are the commonest sites of diffuse osteitis in the long bones, but any of the bones may be involved. Diffuse osteitis and occasional areas of osteoporosis caused by gummatous infiltration are not uncommon and may not cause pain or other symptoms. Sclerosing osteitis of the skull must be differentiated from Padget's disease.

Roentgenographic picture.—The appearance of late bone syphilis on X-ray examination is not specific, and few roentgenologists will make a definite diagnosis of syphilis from the films alone. Yet, in my experience, the diagnosis of probable bone syphilis has been made by the roentgenologists in practically every case of demonstrable late syphilis of the bones seen at Bellevue Hospital. I recently saw a patient with a characteristic swelling of the sternoclavicular joint and marked destruction of the sternal end of the clavicle on X-ray examination. His STS and history were negative for syphilis, but the lesion was so similar to that of gumma of the sternoclavicular joint that antisyphilitic treatment seemed indicated. The process failed to respond to penicillin and arsenicals and was undoubtedly due to some other cause than syphilis. Occasionally great difficulty is encountered in diagnosing degenerative lesions of the bone, but, in general late syphilis of the bone is diagnosed with relative ease by means of roentgenograms when patients are known to have syphilis.

Response to treatment.—Antisyphilitic treatment of bone syphilis usually brings prompt relief of symptoms, but late bone lesions, unlike

early lesions, heal slowly The X ray pictures of a proliferative or sclerosing osteitis will show no change after treatment, except that elevations of the periosteum caused by periostitis may become less prominent. Areas of rarefaction fill in slowly after treatment, and permanent indentations of the bone frequently persist in the case of healed gummas. The case history which follows illustrates an unusual case of widespread syphilis of the bones with dramatic symptomatic relief after penicillin therapy and relatively slow healing, as demonstrated by X-ray examination.

Case history —I X a negress, 42 years of age was admitted to Bellevue Hospital on March 16 1944 For 8 months prior to admission she had noted dull, grinding pain in many bones. The pain was localized to certain areas and did not radiate. There had been marked loss of weight during this time her admission weight being only 77 pounds, and she was so weak that she could walk only a few steps. She had been treated for progressive osteoarthritis. She denied any knowledge of syphilis, and had never had STS.

Physical examination revealed an emaciated, chronically ill negress, with pale mucous membranes. *The other pertinent findings were (1) punched-*out ulcer in the center of the forehead with necrotic bone at the base (2) pea-sized opening of a sinus tract on the left malar prominence of the face (3) two circular scars on the skin of the posterior tip of the left shoulder (4) swelling of the lower third of the left upper arm, including the elbow joint, with inability to extend the joint completely (5) swelling of the right elbow joint with inability to extend the joint completely (6) swelling of the right wrist, with subluxation of the ulnar bone at the wrist and a linear depressed scar of the skin in the lower ulnar region of the right forearm (7) inability to flex the third fourth, and fifth right fingers at the proximal and distal interphalangeal joints (8) diffuse fusiform swelling of both knee joints, especially the left which had a small circular area of darkened skin above *the tibial tubercle (9) the liver* was enlarged three fingers below the costal margin.

The report of the roentgenologists after X ray examination of all the bones was as follows

Skull.—Extensive osteosclerosis involving the cranial bones with areas of destruction of the outer and middle tables.

Upper extremities.—(Right) sclerosing and destructive osteitis involving the middle and lower thirds of the humerus, the lower and upper fourths of the ulna and the upper half of the radius (left) destructive osteitis of lower half of humerus, lower third of ulna and upper fourth of radius, with pathological fracture of radius.

Shoulders.—Destructive and sclerotic changes involving the acromial process of the right scapula and both acromial processes of the scapulas.

Lower extremities.—Sclerosing and destructive osteitis of the lower thirds of both femurs and upper ends of the tibias.

Conclusions.—Findings are those of late syphilis.

Laboratory data.—The complement fixation titer of the blood was 120 the quantitative Kahn test was 512. The spinal fluid examination was normal The blood count was hemoglobin 7.5 gm red cell count, 3,200,000 white cell count, 11,000 polymorphonuclear cells, 62 per cent lymphocytes, 18 per cent large mononuclear cells, 2 per cent transitional cells 18 per cent corrected hematocrit, 41 The serum albumin was 3.5 and the serum globulin 3.4 The blood cholesterol was 129 the nonprotein nitrogen was 20. The urine analysis was normal. The icteric index was 6. An electrocardiogram was normal except for low T waves in all three leads.

Treatment.—The patient was treated from April 4 1944 to April 19 1944 with 20,000 units of penicillin every 3 hours for 120 doses, a total of only 2,400,000 units over a 15-day period. She had no Herxheimer reaction and began to improve on the second day of therapy By the tenth day she was walking up and down stairs, and she had very little pain. When she left the hospital on May 1 1944 she walked well, and there was very little limitation of movement of the joints, in spite of a pathologic fracture of the left radius. She began to gain weight before she left the hospital, and within 6 months after treatment she weighed 120 pounds in April, 1948 she weighed 145 pounds. Her weight when treatment started had been 77 pounds. In December 1944 she took a job which required house cleaning and washing clothes as well as other domestic duties. When last seen on April 5 1948 the blood complement fixation titer was 6 and the quantitative Kahn test was 8. The liver was barely palpable beneath the costal margin.

Comment.—This unusual case of widespread lesions of late syphilis indicates that the index of suspicion for syphilis is still too low the patient received medical care for 6 months and no STS was taken. She had scars of old skin gummas as well as active skin and bone lesions. She had probable late syphilitic hepatitis, since, in spite of a normal icteric index and the smooth contour of the liver the liver became much smaller in size within 1 year after treatment with penicillin. But my chief purpose in presenting the case is to show the slow rate of bone repair as evidenced by X ray examination. Figure 53 shows the left humerus at the time of treatment in April, 1944 Figure 54 shows the same bone in October 1944 at which time the patient was free of symptoms, even though incomplete healing is shown in the roentgenogram of the left humerus. The last X ray picture of the left humerus in April, 1948, is shown in Fig 55 and it reveals increased density of the shaft of the humerus as a result of the reparative process. The patient received no antisyphilitic treatment after her original course of penicillin, and she has had a marked drop in the reagin titers of her blood. Figure 56 shows the bones of the left forearm in April, 1944 In spite of the permanent fracture of the radius, the patient has reasonably good function of the left forearm.

LATE SYPHILIS OF THE JOINTS

Late syphilitic joint disease can be classified as follows

1 Arthralgias usually caused by periostitis adjacent to joints



FIG 53. Marked destructive osteitis, lower half of left humerus of patient with late syphilis.



FIG. 54 Incomplete healing 6 months after penicillin therapy of osteitis shown in Fig. 53

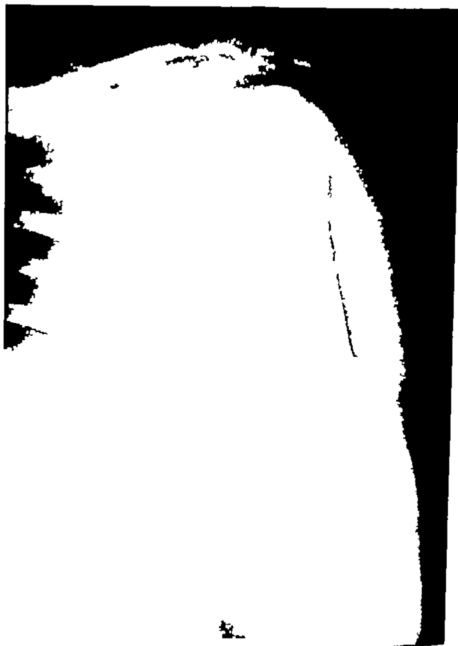


FIG. 55. Complete healing of osteitis shown in Figs. 53 and 54.

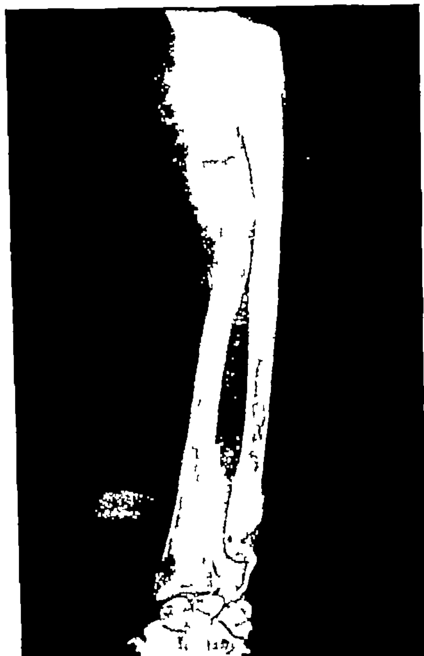


FIG. 56. Destructive osteitis of upper end of radius and lower end of ulna.

2. Gummatous infiltration from gummas arising in adjacent bone, soft tissues, or in the cartilages of the joint
3. Synovitis or arthritis
4. Charcot's joints (neurotrophic joints usually but not necessarily associated with syphilis)

Arthralgias with no swelling of the joints are more common in early than in late syphilis. In both stages, however the pain is probably due to a periostitis of the bones adjacent to the joints. This is especially true of a joint like the knee, movement of which causes tension in the periosteum at the site of tendon insertions.

Gummatous involvement of joints may be caused by gummas originating in the ends of long bones, in the cartilage of the joint, or rarely in the soft tissues surrounding the joint. Pain and local heat are usually slight in proportion to the swelling, and, at times, both are absent. The response to antisyphilitic treatment is usually prompt and striking. Depending on the degree of bone and cartilage destruction prior to treatment, more or less secondary osteoarthritis may develop in the damaged joint.

Synovitis with hydrarthrosis is rarely seen in late acquired syphilis but Chesney Kemp Resnik, and Baetjen have reported cases of syphilitic arthritis with fluid in the joints from which T pallidum was demonstrated on intratesticular inoculation of rabbits with the joint fluid. The arthritis in these cases apparently was confined to the synovial membranes with resulting hydrarthrosis. Pain and local heat were slight in the cases reported. The commonest site of bilateral hydrops in late syphilis is the knee. Congenital syphilis may cause bilateral hydrarthrosis, known as Clutton's joints, usually in the knees or elbows. In such cases large amounts of fluid collect in the joints, causing marked swelling with no pain. Aspiration is followed by rapid reaccumulation of the fluid, but prompt improvement occurs with antisyphilitic treatment.

Charcot's joint.—Although there is no evidence that Charcot's joint is caused by a syphilitic infection of the joint, it seems advisable to describe this curious phenomenon in the section on joint diseases rather than in the discussion of tabes dorsalis which is the usual cause of neurotrophic joints in syphilitics. Ever since Charcot's original article on neurotrophic arthritis, the condition has been recognized as an entity. The phenomenon is characterized by osteophytic changes which cause fragmentation of the bone. Unless at least one fragment of bone is seen on X ray examination the diagnosis of Charcot's joint cannot be made.

Clinically the joint is swollen and is practically painless. It may or may not contain fluid. For reasons which are obscure, Charcot's joint may become stationary showing no improvement or progression or the degenerative process may continue until the joint is little more than a bag of bones.

It is generally believed that the joint deterioration is neurotrophic in origin because it occurs only in association with demonstrable injury of the sensory nerves. Tabes dorsalis and syringomyelia are the commonest conditions with which Charcot's joints are associated, but pathologic changes in peripheral nerves, and even in the hypothalamus, have been accused of being the cause of neurotrophic arthritis. Obviously the true mechanism of the osteophytic changes is unknown. Many individuals with severe tabes dorsalis or syringomyelia escape Charcot's joints. Trauma has been suggested as a contributory cause, but several years ago I saw a woman with 13 Charcot's joints who had developed most of the joint changes after she had become an invalid. In her case, trauma could have had little part in causing the joint pathology. Another patient who has had a mild Charcot's joint of the knee, which has remained stationary for 20 years, has on two occasions injured the knee without further deterioration of the joint. I doubt that trauma plays a significant part in the etiology of Charcot's joint, but neither can I believe that nerve injury alone causes the degenerative changes. Some additional factor such as a deficiency disease, allergy or a toxic condition may be superimposed on the nerve injury.

Fisher and others have suggested that a syphilitic infection of the articular cartilage initiates a Charcot's joint, and that the osteophytic changes are due to syphilis. But, as far as I know, a Charcot's joint has never been reported in syphilis apart from syphilis of the spinal cord or the peripheral nerves. Furthermore, I have never known a Charcot's joint to improve after antisyphilitic treatment, although other observers have reported benefit from antisyphilitic treatment in rare cases. As a matter of fact, we know little more about the mechanism of neurotrophic arthritis than when Charcot first described it, and the condition continues to be one of the unsolved problems of medicine.

SYPHILIS OF THE RESPIRATORY TRACT

Larynx.—Late syphilis of the larynx may appear as a solitary gumma or as syphilitic nodules and ulcerations on the vocal cords, aryepiglottic folds, and epiglottis. A gumma of the larynx may cause sloughing of the cartilages, and stenosis has been reported in some cases after healing

Syphilitic ulcerations of the vocal cords have occurred in several patients on our service. An absolute diagnosis of syphilitic inflammation can rarely be made by laryngoscopy alone, but a therapeutic test will usually establish or rule out syphilitic etiology

Trachea and bronchi.—Gummas of the trachea with treacheoesophageal fistulas have been reported in the older texts on syphilis. I have not seen syphilis of the treachea or bronchi, and it is generally agreed that syphilitic lesions in these structures are exceedingly rare.

Lungs.—Syphilis of the lungs is very rare, but it unquestionably occurs. Wilson and others have reported finding T pallida in lesions of the lungs. The diagnosis during life is exceedingly difficult. As experienced a chest specialist as Amberson, director of the Chest Service at Bellevue Hospital, informs me that he has never made a definite diagnosis of syphilis of the lungs. He has, however had reason to suspect it on occasions. Within the past year a patient was admitted to the Chest Service at Bellevue Hospital who may have had a gumma of the lung Through the courtesy of the Chest Service the relevant facts of the case are presented below

Case history.—P C., a white male, 51 years of age, was admitted to Bellevue Hospital on October 27 1947 He stated that he had been well until about 6 months before admission to the hospital. The first symptoms noted were fatigue and loss of initiative. He felt tired most of the time and had to force himself to work. He later noticed that he was losing weight and reported that he had lost 25 pounds in 6 months. Several months before admission he developed a nonproductive cough which was worse at night and seemed to occur only when he lay on his right side. About 1 month before admission he consulted a physician who took an X ray film of the chest and later referred him to Bellevue Hospital. It was then learned that the patient had had positive serologic tests for syphilis in 1944 and that he had received an unknown amount of antisyphilitic treatment from July 1944 to July 1946.

Physical examination.—The patient was a well-developed white male who did not appear ill. The left pupil was slightly larger than the right, but both pupils reacted to light and on convergence. The fundi were normal. The temperature was 100 F pulse, 80 respiration, 20 and the blood pressure was 120/80. Except for a questionable area of dullness in the right anterior chest from the second to the fourth ribs, the physical examination revealed no abnormal findings.

Laboratory data.—On admission, 2 positive sputum smears for acid-fast bacilli were found, but 19 subsequent smears and 8 sputum cultures were negative, and the first reports were believed to be laboratory errors. The Wassermann, Kahn, and Mazzini tests of the blood were strongly positive. The spinal fluid Wassermann reaction was 4 plus in 0.24 cc amounts, but it was negative in 0.125 cc. The spinal-fluid cell count was 16 per cu mm the

total protein was 96 mgm per cent the colloidal gold was 5443321000. All other laboratory tests, including complete blood count, electrocardiogram urinalysis, nonprotein nitrogen, and alkaline phosphatase, were normal.

X ray examination.—The chest roentgenogram showed a diffuse, dense infiltration extending from the right hilar region outward from the second to the fourth ribs (Fig 57) There was a suggestive rarefaction in the center of the infiltration. When fluoroscoped in the right lateral position, the area of infiltration was localized in the right upper lobe.

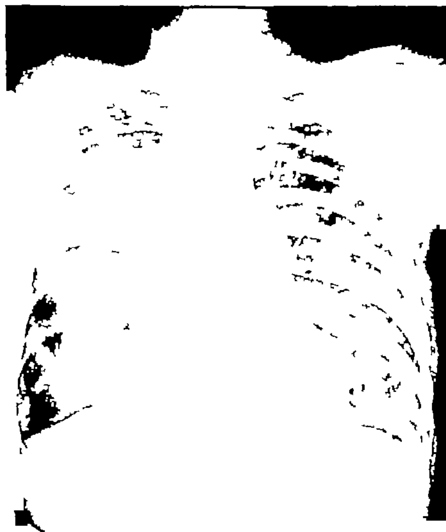


FIG. 57 Possible gumma of lung.



FIG. 58. Healing and scar tissue following penicillin therapy of patient who had a possible gumma of the lung.

Bronchoscopy on November 7 was negative.

Course.—An exploratory thoracotomy was considered, but in view of the fact that the clinical and X ray pictures favored an inflammatory process rather than a malignancy penicillin therapy was started on November 13 1947 The patient received 40,000 units of penicillin in aqueous solution every 3 hours from November 13 to December 3 1947 and from December 11 1947 to January 24 1948 [illegible] total of 19,480,000 units During the peni-

cillin therapy the patient began to gain weight and feel less tired. Repeated roentgenograms of the chest showed a progressive diminution in the size of the infiltrate in the right upper lobe. The last roentgenogram in April, 1948, is shown in Fig. 58.

Comment.—There is no proof that the lung lesion in this case was a gumma, but the history laboratory findings, and response to penicillin make the presumptive diagnosis of gumma a strong one.

SYPHILIS OF THE GASTROINTESTINAL TRACT

Salivary glands.—I have seen two cases of parotitis which may have been caused by late syphilis. The parotid glands were swollen, painless, and nontender The swelling receded with antisyphilitic treatment. Biopsies were not done in either case. Gummas of the salivary glands have rarely been reported.

Esophagus.—Gummas of the esophagus have been reported in the early literature on syphilis, but few if any such reports have appeared within the past decade. The condition is so rare that it is now of little more than historical interest. Kampmeier has reported three cases of esophageal obstruction caused by gummatous infiltration of the diaphragm in the region of the esophageal hiatus. In life, even with the aid of esophagoscopy the diagnosis of syphilis of the esophagus can best be made by a therapeutic test.

Stomach.—Late syphilis of the stomach is not a rarity but the diagnosis is usually difficult. Small gummas of the gastric mucosa may cause ulcers which are indistinguishable on roentgenologic examination from the far more common peptic ulcer Gastroscopy in such cases is difficult and, even in experienced hands, rarely leads to a definite differential diagnosis. Large gummatous infiltrations of the stomach are more readily diagnosed than small gummas. The usual sites of diffuse syphilitic inflammation of the stomach are the midgastric and the prepyloric regions. Involvement of the middle portion of the stomach causes constriction, giving an hour-glass appearance on X ray examinations. Inflammation of the prepyloric region causes narrowing, with stenosis of the pylorus and delayed emptying of the stomach. Gummatous infiltrations of the stomach must be differentiated from scirrhous carcinoma. Experienced roentgenologists have frequently made the probable diagnosis of gastric syphilis when aided by the clinical history and physical findings, but usually carcinoma is the first lesion to be suspected LeWald, in 1931 described the X ray findings in a fairly large series of cases of gastric syphilis. In general the diagnosis can only be suspected from the clinical symptoms and roentgenograms the final decision depends on a thera

peutic test. Every patient with syphilis and gastric pathology deserves a therapeutic test before operation is considered, unless the operation is necessary as an emergency procedure.

Linitis plastica, or leather-bottle stomach was frequently attributed to gastric syphilis in the earlier years of this century but, according to Stokes, O Leary and Lyons, this condition is usually due to a small-cell carcinoma of the stomach. In very rare instances the funnellike stomach known as linitis plastica has resulted from a diffuse syphilitic infiltration of the entire stomach which has left permanent scarring and fibrosis after healing

Syphilitic lesions of the stomach usually respond well to antisyphilitic treatment. The symptoms of pain, indigestion, loss of weight, and gastric retention disappear rapidly but gastrointestinal series usually continue to show permanent defects in the stomach as a result of scar tissue.

Liver —By far the commonest diagnosable manifestation of hepatic syphilis is the so-called hepar lobatum caused by multiple gummas. The lesions may vary in size from microscopic units to large tumors. The liver is usually enlarged, and, when the surface is nodular the presumptive diagnosis of hepar lobatum is relatively easy Unfortunately in some cases of hepatic gummas, the surface of the liver is smooth because of the small size of the gummas or because the lesions are embedded within the liver In such cases, even though an enlarged liver is palpated, the diagnosis of syphilitic hepatitis must await the response to specific treatment. Syphilis is far from the most frequent cause of an enlarged liver Syphilitics may have liver damage from other causes than syphilis, e.g alcoholism, arsenotherapy and malignancy Liver function tests do not help make the differential diagnosis between syphilitic hepatitis and cirrhosis of the liver which is due to other causes. According to Stokes and others, jaundice may occur in late syphilitic hepatitis, but I have rarely observed it. Ascites is frequent in most advanced cases of hepatomegalia and may occur in syphilis of the liver Associated enlargement of the spleen is present in about 50 per cent of patients with chronic liver disease, and the same ratio seems to hold in the case of hepatomegalia due to syphilis. Consequently the diagnosis of late syphilis of the liver frequently depends on a therapeutic test, and even then the diagnosis may continue to be in doubt for several months because the enlarged liver does not decrease in size rapidly after antisyphilitic therapy *If* hepatomegalia is due to syphilis, antisyphilitic treatment will almost always cause a definite reduction in size within several months.

It is still a moot question whether a diffuse syphilitic hepatitis with a

histologic picture similar to that of cirrhosis of the liver can be caused by syphilis. In my experience, the diagnosis of syphilis of the liver has rarely been made at autopsy unless microscopic or macroscopic gummas were present. Stokes, however describes syphilitic cirrhosis of the liver with diffuse fibrosis, and it seems reasonable that this should occur although the pathologic picture may not be specific.

Stokes also describes a diffuse syphilitic perihepatitis involving the capsule of the liver and the peritoneal coverings of the liver and spleen. The serous membranes are thickened, and adhesions form. The symptoms may be those of gall-bladder disease, and laparotomies have been performed for removal of the gall bladder in such cases. Obviously the clinical diagnosis of perihepatitis is difficult, and it is not surprising that errors in diagnosis have been made.

The safe rule to follow in the presence of liver disease associated with syphilis is to give antisyphilitic treatment before considering operation. In view of the possible danger of a Herxheimer reaction or therapeutic paradox, treatment should be started with bismuth. Tucker describes two cases of hepar lobatum treated successfully within recent years with penicillin alone. In all probability penicillin could be used at the beginning of treatment in most cases of liver syphilis, but we had an unfortunate experience with one patient, as noted in the section on Herxheimer reactions in Chap. 7 and Stokes has long warned against Herxheimer reactions in syphilis of the liver

SYPHILIS OF THE SPLEEN

No doubt syphilis of the spleen occurs, but splenomegalia is rarely observed in syphilis except in association with enlargement of the liver Gumma of the spleen has been found at autopsy in rare instances.

SYPHILIS OF THE PANCREAS

Few pathologists are willing to make a diagnosis of chronic interstitial pancreatitis resulting from syphilis. If syphilis causes a chronic pancreatitis, the histologic picture is not characteristic. Reports have been made of rare cases of diabetes mellitus which showed great improvement following antisyphilitic treatment. I have never known the diagnosis of syphilitic pancreatitis to be made at Bellevue Hospital. Gumma of the pancreas has been reported.

SYPHILIS OF THE GENITOURINARY TRACT

Kidney.—Rich reported a fairly characteristic picture of low-grade chronic glomerulonephritis in the kidneys of 29 syphilitic patients who

came to autopsy So far as I know the diagnosis of late syphilitic nephritis has rarely been made during life, and few pathologists have confirmed the pathologic findings of Rich. Gumma of the kidney has been reported at autopsy

Paroxysmal hemoglobinuria.—This condition in which hemoglobin appears in the urine as a result of hemolysis of red blood cells in the circulation, has been attributed to syphilis. There is little proof however that syphilis is directly concerned with the phenomenon, even though the patient has a syphilitic infection. It may occur in syphilitics after exposure to cold as well as in nonsyphilitics.

Bladder.—Gumma of the bladder has been reported, as have gummas in most other organs of the body except the intestines and ovaries. The gummatous infiltration of the bladder causes a chronic ulceration which is best diagnosed by a therapeutic test.

Testicle and epididymis.—A diffuse interstitial orchitis, which may rarely involve the epididymis, is not unusual in late syphilis. The condition is usually unilateral but may be bilateral The involved testicle is enlarged, painless, and firm. If syphilis is kept in mind the diagnosis will be suspected, and it usually can be made without great difficulty Solitary and multiple gummas of the testicle produce nodular lesions. I have records of two patients with gumma of the testicle who were operated on for suspected teratoma. Following antisyphilitic treatment the orchitis subsides, and the testicle becomes smaller but rarely attains a normal consistency on palpation At times involution following treatment causes marked atrophy of the testicle. There is no evidence, however, that such atrophy is due to a Herxheimer reaction.

Ovaries, Fallopian tubes and uterus.—For unknown reasons, syphilis apparently never produces demonstrable lesions in the ovaries and tubes. Authentic reports of syphilitic inflammation in either of these structures are lacking Gummas may occur on the cervix in rare instances, but none has been reported to my knowledge in the body of the uterus.

SYPHILIS OF THE BREASTS

Gummas of the breast have been reported rarely Chronic mastitis has been attributed to syphilis, but there is no reliable evidence that syphilis produces diffuse interstitial changes in the breast tissues.

SYPHILIS OF THE ENDOCRINE GLANDS

Apart from the testicles, syphilis of the endocrine glands appears to be extremely rare. In 1945 Laird in England reported a gumma of the

thyroid, and gummas of the adrenal gland have been found in rare instances. It may well be that the endocrine glands are more frequently involved by syphilis than is generally recognized pathologists rarely report evidence of syphilitic inflammation in these glands, possibly because there is nothing specific about the histologic picture. Simmond's disease, caused by syphilitic involvement of the anterior pituitary gland, has been described. Simmond himself reported 9 cases of probable syphilitic involvement of the hypophysis in 1 700 autopsies in which he examined the pituitary gland The French literature on syphilis contains references to endocrine disturbances which were attributed to congenital syphilis, but the evidence in favor of a syphilitic etiology in the case reports is not convincing

SYPHILIS OF THE PERIPHERAL BLOOD VESSELS

As previously noted, syphilis is prone to affect the small blood vessels, and one of the characteristics of syphilitic pathology is perivascular infiltration. However thromboses of the peripheral arteries, apart from the central nervous system, are rarely due to syphilis. I have seen one patient with gangrene of the toes who improved markedly after antisyphilitic treatment with arsenoxide and bismuth.

TREATMENT OF LATE BENIGN SYPHILIS

In the prepenicillin era it was usual to begin antisyphilitic therapy of all late syphilis with bismuth. Possibly a rare accident due to a Herxheimer reaction or therapeutic paradox would be avoided if bismuth therapy always preceded treatment of late syphilis with penicillin. Preliminary treatment with bismuth for at least 3 or 4 weeks may be advisable, provided patients can be kept under treatment. The difficulty of keeping patients under regular therapy in large syphilis clinics is frequently so great that the danger of losing patients may outweigh that of possible severe Herxheimer reaction or therapeutic paradox. I have seen no evidence of serious damage due to Herxheimer reactions in starting treatment of late syphilis with penicillin except in the one case of possible syphilis of the liver previously mentioned.

Penicillin is the drug of choice for intensive antisyphilitic therapy and all cases of late symptomatic syphilis should receive no less than 4 000,000 units over a period of not less than 2 and preferably 3 weeks. The time dose relationships depend on the penicillin preparation chosen. Aqueous

solutions of 40,000 to 80 000 units should be given every 3 or 4 hours. POB or procaine penicillin in oil without aluminum monostearate can be given in daily doses of 300 000 to 600 000 units, or in doses of 600 000 units three times a week. Procaine penicillin in oil with aluminum monostearate in doses of 600 000 units can probably be given twice weekly but the period of therapy should then be extended for at least 4 weeks. All patients treated should, of course, be kept under frequent observation for at least 2 years. It is improbable that syphilis will relapse after 2 years, but patients should be observed at intervals of at least 6 months for as long as possible.

REFERENCES

CHESNEY A. M KEMP T E. and BAETJER F H. "A Study of the Synovial Fluid of Patients with Arthritis and Syphilis," *J Cl n. Investigation* 3 131 1926

——— ——— and RESNIK, W H. "Syphilitic Arthritis with Eosinophilia Recovery of T Pallidum from the Synovial Fluid, *Bull. Johns H pkins Hosp* 35 235 1924

DELANO, P J "The Pathogenesis of Charcot s Joint," *Am. J Roentgenol.* 56 189 1946

DEXTER, D D and TUCKER, H A. "Penicillin Treatment of Benign Late Gummatous Syphilis, A Report of 21 Cases," *Am. J Syph. Gonor & Ven. Dis.* 30 211 1943

EUSTERMAN G B "Gastric Syphilis," *J.A M.A.* 96 173 1931

FOURNIER, A. *T aité de la Syphilis* J Rueff et Cie Paris, 1899

FREUND, E. Über Syphilis der Gelenke," *Vir h A h. f path. Anat* 289 575 1933

GOLDNER, A. I "Tertiary Syphilis of Ear Nose and Throat," *Arch Otolaryng* 45 463 1947

HARRIS S., and MORGAN H. J "The Isolation of Spirochaeta Pallida from the Lesion of Gastric Syphilis, *J.A M.A* 99 1405 1932.

HOFFMANN E. "Zur Frage der Lues articularis praecox unter dem Bilde der Polyarthritis rheumatica," *Wien. klin W hnsch* 12 1837 1933

KLAUDER, J V "Treatment of Interstitial Keratitis with Particular Reference to the Results of Penicillin Therapy *Am. J Syph. G nor & Ven. Dis.*, 31 569 1947

KUTSHER, G V and WINDHOLZ F "Clinical Radiologic and Pathologic Aspects of Late Syphilis of Lungs Effects f Penicillin Therapy *Am. J Syph Go o & V Dis* 31 166 1947

LAIRD S M "Gumma of Thyroid" *Brit J V n. Dis* 21 162 1945

LARMORE, J L. "Tertiary Syphilis of the Larynx Its Diagnosis, Pathology and Treatment, *J Indiana M.A* 40 638, 1947

LEWALD L. T Roentgen Diagnosis of Gastric Syphilis," *J.A.M A* 96 179 1931

Moore, J E. *Penicillin in Syphilis* Charles C. Thomas, Publisher Springfield, Ill., 1946.
O'Leary P A. and Herrell, W F "Penicillin in the Treatment of Late Cutaneous Syphilis, *Proc Staff Meet., Mayo Clin.*, 19 20 1944
Palmer, W L. Benign and Malignant Gastric Ulcers Their Relation and Clinical Differentiation," *Ann. Int Med* 13 317 1939
——— Schindler, R. Templeton F E. and Humphreys E. W "Case Report of Syphilis of Stomach," *Ann. Int. Med.*, 18:393 1943
Rich A. R. "Pathology of 19 Cases of Nephritis Associated with Acquired Syphilis," *Bull. Johns Hopkins Hosp* 50 357 1932
Schlesinger, H. "Present Status of Clinical Aspects of Syphilis of the Stomach, *Wien. klin Wchnschr.*, 42 861 1929 abstracted in *J.A.M.A.*, 93 885 1929
Schumacher, G A. "Causative Factors in the Production of Laennec's Cirrhosis with Special Reference to Syphilis," *Am. J M Sc.*, 194 693 1937
Singer, H. A., and Meyer, K. A. "Syphilis of the Stomach with Special Reference to Errors in Diagnosis *Am. J Surg.*, 21 1 1933
Symmers D and Spain D M. "Hepar Lobatum Clinical Significance of the Anatomic Changes," *Arch Path.*, 42 65 1946.
Tucker, H A. and Dexter, D D: "Penicillin Treatment of Gummatous Hepatic Syphilis. Report of 2 Cases," *Arch Int M d.*, 78 313 1946.
Wilson J M. Acquired Syphilis of the Lung Report of a Case with Autopsy Findings and Demonstration of Spirochetes," *Ann. Int Med.*, 25 134 1946.

CHAPTER 12

CARDIOVASCULAR SYPHILIS

The term cardiovascular syphilis is used to describe syphilis of the aorta and heart. The myocardium is seldom involved directly by syphilis, but it undergoes secondary changes as a result of the inflammatory process in the aorta and aortic valve. Cardiovascular syphilis is usually classified as a late manifestation of the disease. Exceedingly rare cases of aortitis and aortic insufficiency developing during the first 2 years of infection have been reported. On our service we have had reason to suspect a transient myocarditis in a few cases of secondary syphilis, but there is no pathologic evidence that early syphilis causes a recognizable myocarditis. As most late syphilitic heart disease has its origin in the aorta the pathologic changes caused by syphilis in the aorta and aortic valve will be considered first.

PATHOLOGY OF SYPHILIS OF THE AORTA AND AORTIC VALVE

The ascending or supracardiac portion of the aorta is most frequently involved by syphilis. The arch and descending thoracic portions are the next most frequent sites of inflammatory reactions, and the abdominal aorta usually escapes entirely. Syphilis is by far the commonest cause of inflammation in the aorta and as a rule, the pathologic picture is fairly characteristic.

The inflammation consists of infiltrations of round cells, chiefly lymphocytes and plasma cells, into the media. Perivascular cuffing of the vasa vasorum is always present in both the media and adventitia, and many of the capillaries are obliterated by endarteritis. The elastic fibers and the muscle cells in the media are fragmented and destroyed, and the necrosis is followed by the formation of fibrous tissue. The intima, overlying the areas of the inflammation is hyalinized, thickened and wrinkled and presents a fairly characteristic picture of linear scars or striations which can usually be differentiated macroscopically from the atheromatous

plaques of arteriosclerosis. In time the aorta dilates because of the loss of elastic tissue and the weakening of the wall. The degree and site of dilatation depend on the degree and site of injury. By far the most frequent site of early dilatation is the supracardiac portion, but marked aneurysmal dilatations are likely to occur also in the transverse limb of the arch and the descending thoracic portions.

Aneurysm.—A focal weakness of the wall causes an outpocketing known as a saccular aneurysm. Unless protected by clot formation within the sac, an aneurysm gradually increases in size. Sometimes the sac is completely filled by a clot, and endothelium grows over its surface, thus cutting it off entirely from further contact with the circulating blood. In other cases the outpocketing progresses to very large dimensions, and it frequently erodes the vertebrae, sternum, or ribs.

Ostiostenosis.—The mouths of the coronary vessels in the first part of the aorta may be stenosed by the syphilitic process. At autopsy one or both of the coronary ostia have been found to be greatly reduced in size in some cases of aortitis. Complete closure of one ostium has occurred on occasions. If the stenosis is gradual and confined to one ostium, collateral circulation develops, and the myocardium may be supplied fairly adequately with blood. Ostiostenosis, however usually causes varying degrees of fibrosis in the heart muscle, and it is one of the causes of heart failure in cardiovascular syphilis.

Aortic insufficiency.—The third pathological complication of aortitis is incompetency of the aortic valve caused by a widening of the aortic ring and consequent failure of the cusps to meet on closing. In some cases the aortic cusps are directly involved by the syphilitic infiltration. The edges, especially become thickened and rolled. As a result of the incompetent valve, the myocardium of the left ventricle hypertrophies and the ventricle dilates.

PATHOLOGY OF SYPHILIS OF THE MYOCARDIUM

A diffuse myocarditis attributed to late syphilis has been described in many of the older textbooks on syphilis. Few modern pathologists, however admit the possibility of such a diagnosis. If syphilis is capable of causing a diffuse myocarditis, the pathological picture is in no way specific, except in cases of multiple microscopic gummas. The end result of most inflammations of the myocardium is fibrosis of the heart muscle, which common finding is usually due to causes other than syphilis. So far as I know the diagnosis of diffuse syphilitic myocarditis has never

been made at post-mortem in Bellevue Hospital. I have never read or heard of a pathologist's report of diffuse myocarditis attributed to secondary syphilis, but Schur on our service, has found electrocardiographic changes in a few cases of secondary syphilis which suggest the possibility of a transient myocarditis.

Either single or multiple gummas may occur in the myocardium They vary in size from microscopic to macroscopic units. A diffuse distribution of microscopic gummas in the myocardium is probably the only pathological evidence of a late syphilitic myocarditis.

CLINICAL CLASSIFICATION OF CARDIOVASCULAR SYPHILIS

On the basis of the foregoing description of the pathologic changes caused by syphilis, the classification of cardiovascular syphilis is as follows

1 Uncomplicated aortitis
2 Aortitis with ostiostenosis
3 Saccular aneurysm
4 Aortic insufficiency
5 Gumma of the myocardium
6 Diffuse syphilitic myocarditis which is questionable but may possibly occur in secondary syphilis. Late syphilitic myocarditis is very rare and is probably due to multiple microscopic gummas.

UNCOMPLICATED AORTITIS

Aortitis which does not produce aneurysms and does not involve the *ostia or aortic ring is a relatively harmless, benign manifestation of late* syphilis and is not a cause of heart disease. During life it is diagnosed with difficulty and cardiologists are increasingly cautious about attributing dilatation of the aorta during life to syphilitic aortitis. Dilatation of the aorta can be caused by hypertension and atherosclerosis, and more rarely by hyperthyroidism and rheumatic fever There is nothing specific about the physical signs of aortic dilatation caused by uncomplicated syphilitic aortitis. The systolic murmur and altered second aortic sound which may accompany dilatation of the aorta are not diagnostic of syphilitic aortitis. Furthermore, neither of these signs may be present in patients who have definite dilatation of the aorta. Even when the diagnosis of aortitis is fairly certain from fluoroscopic examination it is usually impossible to determine whether or not the coronary ostia are involved. As a result, in spite of the relative ease with which uncomplicated syphi-

litic aortitis is diagnosed at post mortem, the diagnosis during life is not simple.

The present trend is to diagnose uncomplicated aortitis only in syphilitic patients under 45 years of age, since they are less likely than are older individuals to have atheromatous changes in the aorta. This precaution may be wise, but it does not solve the problem. One sees, in patients over 45 years, so-called fusiform "aneurysmal" dilatation of the aorta which could hardly be caused by anything other than syphilis: the arbitrary age rule would not permit such cases to be classified as syphilitic aortitis. Certainly one cannot diagnose as syphilitic every "aneurysmal" dilatation of the aorta reported by the roentgenologists, but, on the other hand, the possibility and even the probability of aortitis in elderly patients with known syphilis cannot be ignored. In my experience, fluoroscopic examination of patients in the left oblique position, which affords visualization of the ascending aorta, makes it possible in many cases to venture a good guess as to the presence of syphilitic aortitis. Marked atherosclerosis of the aorta can often be identified by the presence of calcified plaques and the tortuosity of the vessel. In the absence of hypertension and definite evidence of atherosclerosis, and in the presence of syphilis, dilatation of the supracardiac portion of the aorta with increased pulsation is highly suggestive of syphilitic aortitis. Certainly it would be a mistake to ignore the probability of aortitis in such cases. On our service we have always made a diagnosis of questionable aortitis in such patients, regardless of age.

Without the aid of a teleoroentgenogram or fluoroscopic examination, a presumptive diagnosis of uncomplicated aortitis cannot be made, nor in most cases can the diagnosis even be suspected. Precordial pain has been reported in uncomplicated syphilitic aortitis, but it is a highly unreliable symptom, and there is no proof that uncomplicated aortitis ever causes pain. I have known patients who had normal-appearing aortas and normal electrocardiograms to complain of precordial pain more often than patients who had definite dilatation of the aorta.

AORTITIS WITH OSTIOSTENOSIS

I have never made the diagnosis of stenosis of the coronary ostia with any feeling of confidence. The signs and symptoms of ostiostenosis are in the main those of coronary sclerosis. Both conditions cause heart disease because of the impaired blood supply to the myocardium; the electrocardiographic changes, when present, are similar in both conditions. Again, I hesitate to rely on symptoms such as precordial pain as sugges-

tive of ostiostenosis. The age of the patient and the presence or absence of peripheral arteriosclerosis are important factors in influencing preferential diagnoses between coronary sclerosis and ostiostenosis, but they are not conclusive. Aortic insufficiency can also cause symptoms similar to those of coronary ostiostenosis. The safe rule is to recognize the possibility of ostiostenosis in any syphilitic who has evidence of aortic dilatation and heart disease not definitely caused by something other than syphilis. To recognize this possibility does not necessarily mean a poor prognosis, but it demands a certain amount of caution in starting antisyphilitic treatment.

ANEURYSM

The commonest sites of aortic aneurysm are the ascending transverse, and descending portions of the arch Occasionally multiple aneurysms occur and at times very large aneurysms of the descending portion of the thoracic aorta are noted on fluoroscopic examination or at autopsy

The signs and symptoms of an aneurysm are dependent on its size and location. Large aneurysms may be suspected at times by finding areas of dullness on percussion, but even in expert hands percussion is not a reliable means of diagnosing aneurysm. The only sure way of not overlooking a saccular aneurysm is to fluoroscope every patient with late syphilis. If X ray examination is not routine, it is inevitable that some aneurysms will be missed, because not all of them cause signs and symptoms.

When symptoms occur they are varied and often bizarre. They are due to pressure of the aneurysm on adjacent structures such as the trachea, large bronchi, lungs, esophagus, pulmonary artery innominate and carotid arteries, parasympathetic and sympathetic nerves, recurrent laryngeal nerves, intercostal nerves, ribs, sternum and vertebrae, diaphragm, and, indirectly the stomach.

The symptoms include pain (which in some cases is severe but oftentimes less continuous and disabling than one would expect considering the size of the aneurysm and the amount of bone erosion present) dyspnea, cough, sputum, hemoptysis, hoarseness, dysphagia choking sensations, and vertigo. The signs, on physical examination, include an area of increased dullness in the chest or beneath the sternum, tracheal tug thrill, cardiac enlargement differences in the blood pressure in the arms (caused by pressure on arteries supplying one arm) dilated veins of the chest and shoulders, paralysis of vocal cords, and rarely pupillary changes as a result of pressure on sympathetic chains.

Diagnosis.—As previously stated, the diagnosis of aortic aneurysm is best made by fluoroscopic examination. The fluoroscope affords a better means of noting the character site, and degree of pulsation of the aneurysm than do routine roentgenograms. The latter however will show the presence of bone erosion better than the fluoroscope. On two occasions I have seen teleoroentgenograms taken in the anteroposterior

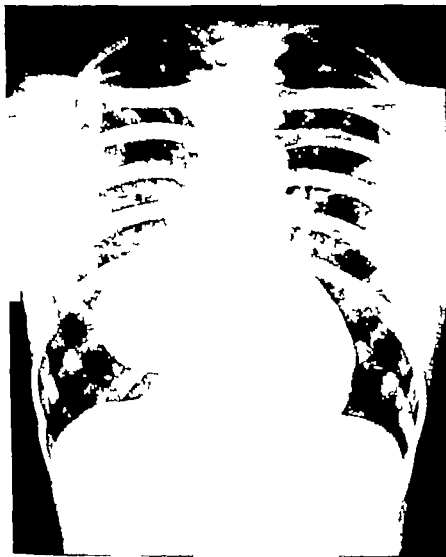


FIG. 59. Dermoid cyst suggestive of aneurysm.

position which showed the presence of mediastinal tumors or dermoid cysts which might easily have been mistaken for an aneurysm. The X-ray film of one of these cases is shown in Fig 59 An aneurysm of the ascending aorta is shown in Fig 60

If routine X ray examinations of the chest are impossible, an aneurysm can be suspected if any of the signs and symptoms previously noted are



FIG. 60. Aneurysm of ascending aorta.

present. One of the most frequent signs of an aortic aneurysm is marked difference in blood pressure in the upper extremities. Hoarseness caused by pressure on one or both recurrent laryngeal nerves is fairly common in aneurysms of the transverse limb of the arch.

Aneurysm of other large vessels.—Occasionally syphilitic aneurysms of other vessels than the aorta are noted. The innominate, carotid, and subclavian arteries are the commonest sites of syphilitic aneurysm, apart from the aorta. Very rarely syphilis is reported to have caused an



FIG. 61. Aortic aneurysm which was "wired" unsuccessfully because the aneurysm was too diffuse.

aneurysm of one of the larger peripheral arteries in the upper or lower extremities.

Prognosis.—The prognosis of aneurysm depends largely on the extent to which the sac is filled by a blood clot. A firm calcified clot which fills the sac prevents further enlargement of the outpocketing and leaves only a tumor mass. Emboli from marantic thrombi in aneurysms rarely if ever occur In the absence of a clot which fills the sac, the prognosis of a large aneurysm is usually poor Death from complications caused by pressure on adjacent structures, especially the bronchi and lungs, is a common termination of aortic aneurysm. Rupture of the aneurysm has also been a frequent cause of death. Cardiac failure may develop in association with an aneurysm, but the failure is usually due to an associated aortic insufficiency

The value of antisyphilitic treatment after an aneurysm has reached large size is difficult to determine. The syphilitic inflammation in the wall of the sac can be healed by treatment, but this does not necessarily prevent further enlargement of the sac. From the point of view of antisyphilitic treatment, prevention of an aneurysm is the major objective, and great progress has been made within the past 20 years in this respect. We see many fewer aortic aneurysms at Bellevue Hospital now than we did 10 years ago. There is no reason to withold antisyphilitic therapy in cases of even very large aneurysms. Treatment should be started with bismuth because of a possible serious Herxheimer reaction, and penicillin is given after the course of bismuth.

Operative treatment.—A number of years ago Blakemore introduced an operative procedure for producing a clot in saccular aneurysms. A thoracotomy was done, the aneurysm located, and wire inserted into the sac and coiled up within it. In selected cases where the opening of the sac into the aortic lumen was not large, this procedure was successful. Blood clotted about the coiled wire and prevented further enlargement of the sac, and in some cases this caused relief of symptoms. An unusual picture showing the presence of the coiled wire in the aneurysm of one of our patients who was operated on by Dr Blakemore is shown in *Fig 61* * Apparently this patient never achieved a good clot within the aneurysm, but in other cases where the outpocketing of the aorta formed a distinct sac, considerable relief of symptoms was obtained.

* The photograph does not show the wire as clearly as the film. The figure is included to illustrate the failure of wiring an aneurysm which does not form a localized sac.

AORTIC INSUFFICIENCY

The major cause of heart disease in cardiovascular syphilis is aortic insufficiency or regurgitation Apart from syphilis, the two chief causes of aortic insufficiency are rheumatic heart disease and arteriosclerosis. A differential diagnosis between these three possible etiologic factors is occasionally difficult, but, in the main syphilitic heart disease with aortic insufficiency is the easiest to diagnose of all the manifestations of cardiovascular syphilis.

Incompetence of the aortic valve permits blood to regurgitate into the left ventricle during diastole. The regurgitated blood as well as the normal ventricular content must be pumped out during systole. As a result, the left ventricle has to beat more powerfully the muscle hypertrophies, and the ventricle dilates blood is forced out of the ventricle with greater momentum causing an increased systolic blood pressure during diastole the peripheral vessels contain less blood and an associated peripheral vasodilatation usually occurs, causing a low diastolic blood pressure.

Signs.—If the foregoing train of events is remembered, the signs of aortic insufficiency will be readily understood, and usually they can be recognized without difficulty Regurgitation of blood from the aorta to to the left ventricle produces a diastolic murmur and the increased pulse pressure gives a variety of signs.

Diastolic murmur—In most cases the diastolic murmur of aortic insufficiency is easily audible and fairly characteristic. It is usually heard throughout diastole as a fairly high-pitched blow which is louder at the beginning óf diastole than at the end. Occasionally a very brief high-pitched murmur is heard only at certain areas at the base of the heart. This localized murmur is easily missed It may be audible only over the second intercostal space to the right of the sternum (Erb's point) but just as frequently it may be heard only over the aortic area to the left of the sternum or over the sternum itself Fortunately such a localized murmur is not the rule in aortic insufficiency

In my experience, over 75 per cent of patients with syphilitic aortic insufficiency have had blowing diastolic murmurs which were transmitted downward and to the left over the entire precordium to the apex. In the great majority of cases there was an associated systolic murmur giving a to-and-fro blowing sound. The second aortic sound may not be heard in such cases. At times a diastolic murmur is heard at the base and cannot be followed downward over the precordium but is again heard at the

apex (Austin Flint murmur) The presence of the diastolic murmur at the base and evidence of increased pulse pressure in such cases is diagnostic of aortic insufficiency whether or not an associated mitral stenosis is present. A diastolic murmur heard only at the base and apex, associated with enlargement of the left ventricle and no sign of an enlarged left auricle or prominent pulmonary conus on X ray examination, is usually an Austin-Flint murmur

Increased pulse pressure—The relatively high systolic and low diastolic blood pressure caused by aortic regurgitation is manifested not only by blood-pressure readings but also by the character of the pulse. A water hammer pulse is frequently seen as well as felt. Pulsations of the arteries in the neck and in the region of the clavicles are usual in aortic insufficiency In many cases incompetency of the aortic valve can be suspected merely by observing the pulsations in the neck and supraclavicular areas. On palpation, the sharp slap of the pulse against the finger is followed by an apparent collapse of the vessel (Corrigan's pulse) On auscultation over the larger arteries, especially the femoral arteries, a water hammer pulse may give a "pistol-shot" sound.

Occasionally aortic insufficiency is found in patients with normal pulse pressure. Presumably the incompetency of the aortic valve in these cases is not great. Yet I have known patients to die in heart failure with very little evidence of increased pulse pressure, although they had enlarged hearts and a diastolic murmur at the base. The probability is that such patients had coronary sclerosis or ostiostenosis, and that aortic insufficiency alone was not the cause of heart failure.

Symptoms.—Most individuals with aortic insufficiency have no symptoms until the left ventricle begins to fail, in which case the symptoms are those of diminished cardiac reserve. The lack of symptoms caused by the incompetent aortic valve prior to beginning heart failure is unfortunate in one important respect the patient is unaware of his injured heart and fails to seek medical aid until late in the course of the disease. Occasionally patients are made aware of the increased pulse pressure by pulsating throbs felt in the chest, neck, and head, or by severe palpitation. In most cases, however it is surprising how few symptoms are caused by the water hammer pulse.

Differential diagnosis.—A diastolic murmur at the base and increased pulse pressure associated with a dilated aorta and an enlarged left ventricle usually suffice to make the diagnosis of syphilitic aortic insufficiency In the absence of positive STS or other evidence of syphilis, however the diagnosis of syphilitic heart disease should be made with caution. The fact that negative STS have been reported in as high as 20 to 25 per cent of

patients with cardiovascular syphilis raises the suspicion that the heart disease in some cases may have been due to other causes than syphilis. I have rarely found negative STS in patients with cardiovascular syphilis unless antisyphilitic treatment had been given 5 or more years before the patient became seronegative. Even in known syphilitics it is occasionally impossible to differentiate between aortic insufficiency caused by syphilis and that caused by rheumatic fever Dilatation of the aorta is sometimes minimal or absent on fluoroscopic examination of patients with syphilitic aortic insufficiency and the presence of positive STS does not preclude the possibility of other types of heart disease. I have occasionally made errors of diagnosis in differentiating between syphilitic and rheumatic aortic insufficiency and I have known cardiologists to make similar errors. A recent case in Bellevue Hospital illustrates the difficulty that may be encountered in making a differential diagnosis.

Case history —F F., a white woman 47 years of age, was admitted to a Medical Service of Bellevue Hosp tal for the first time on November 12, 1944 because of congestive heart failure. Her past history included a bout of acute polyarthritis at the age of 13 which had been diagnosed as rheumatic fever Heart disease was discovered 11 months prior to admission, and for 7 months before admission she had been treated in a clinic with digitalis, ammonium chloride, and mercurial diuretics. She had no knowledge of syphilis, and she had received no antisyphilitic treatment.

The abnormal cardiac findings were systolic and diastolic murmurs over the precordium, heard best over the aortic area. One examiner felt a thrill over the aortic area. The cardiac rhythm was regular The blood pressure was 160/50. X-ray examination revealed the heart to be triangular in shape, enlarged in all diameters." The Wassermann reaction of the blood was 4 plus. A diagnosis was made of rheumatic heart disease with aortic stenosis, aortic insufficiency mitral insufficiency and mitral stenosis.

One year later November 17 1945 she was readmitted to the medical service in congestive heart failure. In the year between these admissions she had been f llowed in the medical clinic, and digitalis and mercurial diuretics were taken regularly Cardiac findings were unchanged, and the diagnosis again was rheumatic heart disease. The Wassermann reaction of the blood was again positive, and the patient was referred to the syphilis clinic for treatment.

Between February 28, 1945 and February 6 1946, she received 18 bismuth and 18 arsenical injections.

The patient was admitted to the hospital for the third time in congestive heart failure on February 13 1946. After the usual treatment for heart failure, she was transferred to the Syphilis Service. A spinal-fluid examination revealed a Wassermann titer of 96 2 cells per cubic millimeter total protein 56 colloidal gold 5 7 7.5 8.5 9 8.5 7.5 7.5 6 3.5 (total 70) It was considered that the murmurs were more suggestive of aortic insufficiency alone than of aortic insufficiency and mitral stenosis, and syphilis was suggested

as the cause of the heart disease. A teleoroentgenogram at this time, however revealed the heart to be enlarged in all diameters, with accentuation of the pulmonary conus. The configuration was believed to be that of both aortic and mitral disease. Because of the X ray findings and the history of polyarthritis in childhood, a definite diagnosis of syphilitic heart disease could not be made, but it was still considered a possibility on our service and the patient was treated with 4 000 000 units of penicillin. She had neurosyphilis as proved by the spinal fluid findings.

She was admitted to the Medical Service in congestive heart failure for the fourth and fifth times in June, 1946, and March 1947 In the intervening periods she had continued to receive digitalis and diuretics, but she was never free from congestive failure symptoms and signs. On these admissions the X ray reports were as follows

June, 1946—"Widening of the supracardiac aorta. Esophogram does not reveal any compression deviation, or filling defect. The heart is enlarged considerable prominence of the left auricular appendage.

March, 1947—"Configuration of heart suggests mitral valvular disease"

Because of a pulmonary infection in June 1946 she received 3 000 000 units of penicillin from June 7 to June 14 1946.

On May 3 1947 the patient was admitted to the Medical Service in a semicomatose condition, with a history of having fallen unconscious 4 hours before admission. She had a right hemiplegia and facial palsy with positive Babinski sign on the right. The cardiac rhythm was totally irregular She died on May 11 1947 (age 50)

Final diagnosis on the Medical Service was rheumatic heart disease with AS AI MI MS with auricular fibrillation and death from cerebral embolus. It was considered that her course was typical of rheumatic heart disease as auricular fibrillation and mural thrombi in the auricle are relatively rare in syphilitic heart disease.

Necropsy findings however revealed syphilis of the aorta, with involvement of the aortic valve resulting in marked insufficiency The mitral valve was normal. There were infarcts of the brain, lungs, spleen, and kidneys due to emboli from mural thrombi in the left auricle. No evidence of rheumatic heart disease was found.

Prognosis.—Cardiologists usually see cases of syphilitic aortic insufficiency only after symptoms of a failing heart have developed. As a result, the prognosis of syphilitic aortic insufficiency has been reported in past years as especially gloomy Actually however there is increasing evidence that many patients live for years with syphilitic aortic insufficiency before signs and symptoms of a failing heart are apparent. Within recent months I have seen 3 patients with aortic insufficiency who were known to have had an incompetent aortic valve for from 14 to 15 years. One had had no antisyphilitic treatment because he refused to admit the diagnosis of syphilis. The other 2 had had very irregular

treatment with bismuth only None of the 3 had had an attack of heart failure, and all 3 were working when I saw them. I do not know the average length of time that patients live after the onset of aortic insufficiency before symptoms of diminished cardiac reserve develop In most cases it is impossible to discover when the aortic insufficiency had its onset. The medical literature on both heart disease and syphilis contains no reliable statistics on this point. Numerous statements have been made that 80 per cent of patients with signs and symptoms of a failing heart caused by syphilitic aortic regurgitation die within 2 years. Reader and his coauthors, in a recent report from New York Hospital, give evidence that the prognosis of symptomatic as well as asymptomatic cardiovascular syphilis is better than has generally been believed. Our experience at Bellevue Hospital accords well with their report. It is true, however that the prognosis in patients who have had one or more attacks of heart failure because of syphilitic aortic valve disease is poor I have known several patients to live more than 6 years after the first attack of heart failure, but they are exceptions.

Obviously the earlier antisyphilitic treatment is given in the course of cardiovascular syphilis, the better the prognosis. In few conditions, however is the prognosis more difficult to evaluate than in that of syphilitic aortic insufficiency prior to the development of heart failure. The significant variables which must be considered in any study of syphilitic aortic insufficiency include

1 Age of the patient
2 Duration of syphilis
3 Age when demonstrable aortic valve disease started
4 Presence and degree of ostiostenosis and atherosclerosis of the aorta
5 Presence of associated diseases, especially arteriosclerosis and hypertension
6 When, what kind, and how much antisyphilitic treatment was received
7 Time, in relation to antisyphilitic treatment, when the first symptoms of diminished cardiac reserve developed
8. Type of work done. Heavy labor is known to influence adversely the course of all heart disease. (Kampmeier and Combs have published an excellent article on the effects of heavy labor on the prognosis of syphilitic aortic insufficiency)

Unless all or most of the above factors are known and taken into consideration, statistics on the prognosis of syphilitic aortic insufficiency are

not very reliable. Few if any cardiac or syphilis clinics have information on most of the above factors in a sufficient number of patients for statistical analysis. Estimates of the influence of antisyphilitic treatment on life expectancy after syphilitic heart disease has developed, are consequently very rough approximations and cannot be taken too seriously. Nevertheless, in the absence of more reliable data, it would be a mistake to ignore such information as is available. The data reported by Moore at Johns Hopkins Hospital, and by the Cooperative Clinic Group indicate that antisyphilitic treatment has prolonged the life expectancy of patients with cardiovascular syphilis, and our findings at Bellevue Hospital are in accord with this general conclusion, although I can venture no opinion about the average length of time added to the lives of patients with aortic insufficiency as a result of antisyphilitic therapy.

GUMMA OF MYOCARDIUM

As previously noted, microscopic or macroscopic gummas may develop in the myocardium. The diagnosis is rarely made during life, and in most cases it cannot even be suspected unless the atrioventricular bundle is involved, in which case heart block develops. Gummas of the myocardium may be solitary or multiple. Healing produces scars consisting of fibrous tissue. From reports of post-mortem examinations, gummas of the myocardium are an infrequent cause of heart disease.

DIFFUSE SYPHILITIC MYOCARDITIS

Although there is no pathologic evidence that early syphilis causes a diffuse myocarditis, occasionally electrocardiographic changes during secondary syphilis suggest that the myocardium may be involved. If it occurs at all, early syphilitic myocarditis is apparently transient and leaves no significant permanent damage.

In June, 1946, a white male, 24 years of age, was admitted to our service with secondary syphilis and auricular fibrillation. He gave no history of rheumatic fever and denied any symptoms of heart disease. Both the aorta and heart were normal in size and shape. An electrocardiogram taken before antisyphilitic treatment was started revealed auricular fibrillation and inverted T waves in leads II and III. He continued to have auricular fibrillation for 2 days only after penicillin therapy was started. Within a week after the onset of antisyphilitic therapy his electrocardiograms were completely normal. No cause other than early syphilis could be found for the auricular fibrillation and T wave changes. Following this case, Schur took a series of electrocardiograms on a

number of patients with secondary syphilis. Occasional T wave changes which became normal following antisyphilitic treatment were noted. The possible occurrence of myocarditis in early syphilis may be of more academic than practical interest because there is no evidence that secondary syphilis causes permanent damage to the heart. It is impossible, however to overlook the possibility that secondary syphilis may cause nondestructive inflammatory changes in the heart muscle in occasional cases.

That late syphilis ever causes a diffuse myocarditis, apart from multiple gummas, is highly improbable. During the past 15 years reports of a diffuse syphilitic inflammation of the myocardium at autopsy are so rare as to be negligible. A diffuse fibrosis of the heart muscle is a common finding at post mortem examinations, but it is usually due to coronary vascular disease, healed rheumatic or other types of myocarditis. Syphilitic ostiostenosis, like coronary arteriosclerosis, may cause fibrosis of the myocardium, but there is little reason to believe that late syphilis causes diffuse inflammation in the cardiac muscle apart from gummas.

TREATMENT

The treatment of cardiac symptoms caused by syphilis is largely that of heart disease in general. Failing hearts should be treated with digitalis mercurial diuretics are of great value when there is the slightest tendency to edema. Antisyphilitic treatment is indicated in most cases that have had inadequate previous therapy

The possible danger of a Jarisch-Herxheimer reaction in the treatment of cardiovascular syphilis was discussed in previous chapters. In spite of the fact that I have had no occasion to be alarmed because of a Herxheimer reaction in the treatment of syphilitic heart disease, it is unquestionably a safe rule to begin therapy in previously untreated cases with bismuth and iodide. On our service we have given only one injection of bismuth subsalicylate in oil every 5 days for three doses as preliminary therapy but it may be wise to extend the bismuth treatment to 6 weeks. Potassium iodide in doses of at least 1 gm three times a day might well be given in addition to the bismuth.

On our service at Bellevue Hospital, Dr Gerald Flaum has been chiefly responsible for the care of patients with cardiovascular syphilis. I am indebted to him for the following report on the penicillin therapy of patients who were treated between March, 1944 and January 1948.

Results of penicillin therapy of cardiovascular syphilis at Bellevue Hospital.—Thirty-nine patients with definite cardiovascular syphilis were treated with penicillin 30 had aortic insufficiency and 9 had aneurysm of the aorta. An additional 22 patients who probably had cardiovascular syphilis received penicillin therapy 18 had a dilated aorta and were believed to have uncomplicated aortitis, and 4 had aortic insufficiency but rheumatic fever could not be excluded as the cause. No untoward reactions were noted in any of the 61 patients during penicillin therapy

Of the 30 patients with aortic insufficiency 8 had aneurysmal dilatation of the aorta, and 1 had a saccular aneurysm in addition to aortic valve disease 8 had received no previous antisyphilitic treatment, and only 3 had received as many as 20 injections of bismuth and 20 of arsenical drugs. Of the 8 patients who had had no previous antisyphilitic treatment, 3 were given no preliminary treatment with bismuth before starting penicillin the remaining 4 received three injections of 0.2 gm bismuth subsalicylate in oil at 5-day intervals before penicillin therapy was started. Penicillin was given in full dosage from the beginning of treatment (30 000 to 50,000 units in aqueous solution every 3 hours) The total dosage varied from 3 000 000 to 6 000 000 units. Of the 30 patients, 3 had had several previous attacks of congestive heart failure. One did not respond to digitalis and mercurial diuretics after admission to the hospital, and she was still in congestive heart failure when treated with penicillin. She died 5 weeks after penicillin therapy was completed. Another who had had three previous attacks of congestive heart failure died 2 months after treatment with penicillin in his fourth attack of heart failure. The third patient, during treatment, had two bouts of nocturnal paroxysmal dyspnea similar to previous attacks, but 3 months after treatment he denied further attacks of paroxysmal dyspnea and was fairly well compensated. In addition to the 2 deaths from congestive heart failure, 3 additional patients have died since the treatment with penicillin. One died 12 months after treatment, following an operation for gall bladder disease a second died of unknown cause 15 months after treatment, although she had delivered a normal child 10 months before her death and 5 months after penicillin therapy was completed the third died 15 months after treatment as a result of cerebral embolus. Of the remaining 25 patients, the status of 6 was unknown 5 were followed up for only 3 months, and the remaining 14 were observed from 6 to 44 months. When last observed 20 and 24 months after treatment, 2 of the 14 were worse, 5 were unchanged after 6 to 44 months, and 7 claimed to be better Of the 7 who claimed to be improved after treatment, 1 had

denied symptoms of diminished cardiac reserve on admission but stated, after treatment, that he previously had had dyspnea and palpitation at work and that these symptoms had disappeared after treatment 3 had complained of dyspnea on exertion (1 with precordial pain) 1 described dyspnea on exertion and nocturnal paroxysmal dyspnea, and 2 had had one attack of congestive heart failure and subsequent complaints of nocturnal paroxysmal dyspnea. Both of the last 2 patients were taking digitalis at the time of penicillin therapy and have continued it since.

All 7 patients who claimed definite improvement of their cardiac symptoms following penicillin therapy were working at the time of this report and they stated that they were able to do more work with less discomfort than before treatment. The most striking improvement occurred in the 3 patients who described paroxysmal dyspnea (2 had had one attack of congestive heart failure) before treatment and who denied subsequent attacks 10 18 and 36 months after treatment. The improvement noted in these patients is not easily explained as resulting from penicillin. The antisyphilitic therapy should have arrested the syphilitic inflammatory process in the aorta, but it is difficult to attribute a definite increase in cardiac reserve to the arrest of such a process. The aortic valves remained incompetent, and it may be that the improvement claimed by the patients was due less to the direct effect on the heart than to the general improvement frequently noted after antisyphilitic treatment. Of the 7 patients, 3 also had active neurosyphilis.

Only 1 of the 9 patients who had aneurysm of the aorta had symptoms at the time of penicillin therapy This patient had secondary pulmonary changes, caused by pressure on the left main bronchus, and died of pulmonary disease 6 months after treatment with penicillin. Three of the patients had had large amounts of previous antisyphilitic treatment with bismuth and arsenicals, but they had active neurosyphilis when treated with penicillin 3 had had no previous antisyphilitic treatment the other 3 had had small amounts of therapy Of the 9 patients, 8 received a total of 3 000,000 to 6,000,000 units of penicillin in aqueous solution, injections being given every 3 hours 1 received 9,000 000 units of penicillin in oil and wax (daily injections of 600 000 units for 15 days) With the exception of the 1 patient who died, the others had no symptoms attributed to an aneurysm.

The patients who had probable uncomplicated aortitis had no reaction during penicillin therapy and have continued to be asymptomatic since treatment. The 4 patients with aortic insufficiency in whom a differential diagnosis between syphilitic and rheumatic heart disease could not be

CHAPTER 15

NEUROSYPHILIS

No aspect of syphilis presents a more fascinating study of the variegated manifestations of the infection than neurosyphilis. Not only can syphilis cause most of the signs and symptoms known to neuropsychiatry but the pathologic processes in the central nervous system also show a variety of inflammatory and degenerative changes. The two classical diseases, general paresis and tabes dorsalis, are both caused by syphilis, but the pathologic picture in each is quite different. Because the syphilitic changes in the central nervous system may be diffuse or focal, there is almost no limit to the variety of clinical manifestations that may be due to neurosyphilis.

GENERAL FEATURES OF THE PATHOLOGY OF NEUROSYPHILIS

The pathologic changes in syphilis of the central nervous system are both inflammatory and degenerative. The process in the meninges and small blood vessels is inflammatory with subsequent thickening of the membranes. The early acute meningitis of secondary syphilis apparently heals with very little thickening of the meningeal membranes, but late syphilis causes thickening and oftentimes adhesions. The parenchymatous changes caused by syphilis are chiefly degenerative and are often secondary to inflammation of the meninges and small vessels.

In meningovascular syphilis the inflammation is focal rather than diffuse localized areas of arachnoiditis, pachymeningitis, and vascular changes occur at various sites. In addition there may be foci of round-cell infiltration in the brain and spinal cord together with the usual perivascular collars of small mononuclear cells.

General paresis is a diffuse meningoencephalitis. Pachymeningitis, with marked thickening of all the meningeal membranes, is usually present. Within the brain, perivascular infiltration is prominent and there are varying degrees of round-cell infiltration throughout the cerebral hemispheres. Atrophy of the nerve cells and fibers always occurs, but it varies

greatly in degree, as do the inflammatory changes. The degeneration of the parenchyma is followed by gliosis. In some cases T pallida are easily found in the brain, and in others the treponemes are found with difficulty

In tabes dorsalis, spinal paraplegia, and optic atrophy the demonstrable pathologic changes are almost entirely degenerative. The T pallidum has rarely been found in syphilitic degeneration of the posterior columns of the spinal cord (tabes dorsalis) of the lateral pyramidal tracts (spastic paraplegia) and of the optic nerves (primary optic atrophy) In all of these structures the essential lesion is not characteristic of syphilis, since the usual signs of syphilitic inflammation are absent. The first change noted by pathologists is a demyelinization Later the axis cylinders disintegrate In advanced cases the entire medullary sheath may disappear The pathologic nerve tissue is replaced by gliosis and there is a proliferation of astrocytes. The small vessels show some thickening, but the perivascular infiltration so common in syphilitic inflammations is absent in the degenerative changes of the posterior columns, lateral pyramidal tracts, and optic nerves. In tabes dorsalis the posterior nerve roots as well as the dorsal ganglia may be involved by the degenerative process.

The pathogenesis of tabes dorsalis, spinal spastic paraplegia and primary optic atrophy has long been an unsolved problem. Inflammatory changes of the posterior root ganglia would cause degenerative changes of the afferent fibers in the posterior column, but, according to Boyd, no such inflammatory lesion has been found. The most plausible theoretical cause of the degenerative changes would be inadequate blood supply caused by vascular damage, but the pathologists do not admit this possibility on the basis of their findings. Consequently it has been suggested that tabes dorsalis, spastic paraplegia, and optic atrophy are due to deficiency diseases associated with syphilis or to toxins elaborated by treponemes in the body None of the theories has the support of any scientific evidence at present. Tabes dorsalis is notoriously a disease of the asthenic or slender individual (also called the ectodermic type of constitution) but this observed fact does not explain the pathogenesis.

In spite of the paucity of observed inflammatory changes in syphilitic degenerations of the posterior columns, lateral pyramidal tracts, and optic nerves, the spinal fluid of patients who have active forms of these diseases, with possible rare exceptions, contains increased cells and protein, which are indicative of an inflammatory process. As a matter of fact, the possibility of clinical improvement following antisyphilitic therapy of all

three diseases is usually better in patients who have increased cells and protein in the spinal fluid than in those whose spinal fluid indicates no activity of the infection. Consequently syphilitic inflammation cannot be ruled out as the primary cause of the degenerative changes in tabes dorsalis, syphilitic spastic paraplegia, and primary optic atrophy

DIAGNOSIS OF NEUROSYPHILIS BY SPINAL-FLUID EXAMINATION

Because the clinical syndromes of neurosyphilis can be caused by diseases other than syphilis, I have no hesitancy in making the dogmatic statement that active neurosyphilis, with rare exceptions, can only be diagnosed by spinal-fluid examination. Obviously the diagnosis can be suspected from the clinical signs and symptoms in many cases, but even the clinical syndromes of paresis and tabes dorsalis may occasionally have causes other than syphilis, as witness the terms pseudoparesis and pseudotabes. *Pupillary changes are usually characteristic of neurosyphilis, but* they may have another etiology Adie's syndrome, which will be described later is not an extremely rare phenomenon. Within the past few years Dattner has demonstrated several cases of this syndrome that were originally diagnosed as tabes dorsalis. Manic-depressive psychoses have been mistaken for general paresis merely because of the known presence of syphilis, in spite of normal spinal fluid findings and the correct diagnosis of general paresis has been missed not infrequently for the lack of a spinal fluid examination. Within the past year Dattner has shown me two patients with known syphilis, erroneously diagnosed as neurosyphilis in spite of normal spinal fluid examinations, who were found to have brain tumors. Except in very rare cases of possible syphilitic cerebral vascular thrombosis or hemorrhage, I do not believe that an active syphilitic infection of the central nervous system is present when the spinal-fluid findings are normal. If there are exceptions to this rule, they are indeed rare. *By normal spinal fluid findings, I mean that the specific tests for* syphilis, cell count, and protein determinations must be normal. There is fairly general agreement among most syphilologists that active syphilis of the central nervous system cannot be *diagnosed when all of the spinal* fluid tests are normal. But in past years neither neurologists nor syphilologists have agreed concerning the activity of neurosyphilis when the spinal fluid contained normal cells and protein but showed positive specific reactions for syphilis.

DIAGNOSIS OF ACTIVITY OF NEUROSYPHILIS

In Chap. 4 it was pointed out that the spinal fluid tests as a rule afford a reliable index of the activity of neurosyphilis. This concept was first described by Dattner while working in Wagner Jauregg's clinic in Vienna and was later redescribed in this country by Dattner and myself. As a result the phrase "Dattner Thomas spinal-fluid concept" has appeared in some of the recent literature on neurosyphilis. The label is unimportant, but the understanding of the concept is. The important point is the recognition that the spinal-fluid tests do afford a means of differentiating between active and inactive syphilitic infections of the central nervous system.

In 1942, Dattner and I published an article on "The Management of Neurosyphilis." In it we stated that the best guide to the activity of a syphilitic process in the central nervous system is the spinal-fluid cell count. Provided that the Wassermann test of the spinal fluid was positive, we stated that arrest of the syphilitic process in the central nervous system could be determined by observing the entire pattern of spinal-fluid tests. We contended that inactivity of neurosyphilis is indicated by a normal cell count and a persistent trend toward normal values of all the other abnormal quantitative tests of the spinal fluid. This concept met with considerable skepticism from both neurologists and syphilologists, who claimed that neurospyhilis might be progressive in spite of normal cell counts. The skepticism was not surprising. When Dattner first outlined his concept to me in 1938, I also was dubious and had the impression that I had seen cases of neurosyphilis progress in spite of normal cell counts. Furthermore, I questioned the reliability of cell counts and total protein determinations as done not only on my own service but in other clinics and hospitals. I recognized, however, the importance of Dattner's concept. If it could be verified, we would have objective guides to the diagnosis and treatment of neurosyphilis that were otherwise lacking. I had been searching for reliable criteria for determining the duration of treatment of neurosyphilis and had not found any that were satisfactory. The favorite phrase among many of us who were treating neurosyphilis at that time was that the treatment of neurosyphilis had to be individualized, meaning that no routine schedule of therapy could be advised, and that each case must be treated as a separate problem. Admirable as is the precept that every patient should be treated as a special problem, when it came to the details of treatment in a given case, the practice of

individualizing therapy in neurosyphilis actually meant very little. Spinal-fluid Wassermann tests remained positive for years in most cases what were the criteria for continuing therapy in such cases? The only criteria we had to guide us were the clinical signs and symptoms, and I was well aware that they were not reliable guides to the success or failure of anti syphilitic treatment in most cases of neurosyphilis. Therefore, Dattner's concept was one of major importance.

To verify it, on our service, the first thing we had to do was to make certain that cell counts and total proteins were done accurately At the beginning this meant that one of the members of the staff had to do the tests under the direction of Dattner Later technicians were trained, and their work proved highly satisfactory Within 2 years, I was convinced of the accuracy of Dattner's conclusions. When cell counts are done carefully very few untreated patients with positive spinal-fluid Wassermann reactions will be found to have normal cell counts. The occasional untreated case that has a positive spinal-fluid Wassermann test and normal cell count is usually one of "burned-out" tabes dorsalis, on which antisyphilitic treatment has no demonstrable effect. Few rules in medicine are absolute, and I do not claim that active neurosyphilis is never present in untreated patients with positive spinal-fluid Wassermann reactions and normal cell counts. However within the past 10 years I have rarely observed such a case, and I cannot recall more than 10 cases where active neurosyphilis could be reasonably suspected in the absence of increased cells in the spinal fluid In early syphilis the first sign of involvement of the central nervous system is increased cells, and the Wassermann test may still be negative. I have known several exceptions to this rule which may or may not have been due to technical error In the few exceptions it was impossible to repeat the spinal-fluid examination, but our records show several cases of early syphilis with positive spinal-fluid Wassermann tests and normal cell counts. In such cases the process in the central nervous system could scarcely be inactive if the reports of the Wassermann tests were accurate. In general, however a spinal fluid with normal cells can be called inactive. Such terms as near normal have no meaning unless each different test is reported. The terms active and inactive refer to abnormal and normal cell counts, respectively In late neurosyphilis, positive spinal-fluid Wassermann tests and increased cells are usually associated with increased total protein. The new Lange colloidal gold curve, as mentioned in previous chapters, is extremely sensitive, and it is practically never normal in an "active spinal fluid" it may continue to be abnormal for years in an inactive case.

With the foregoing explanation, the so-called Dattner Thomas concept of spinal-fluid findings in neurosyphilis can be summarized as follows

1 Signs and symptoms of neurosyphilis are not reliable criteria of the activity of a syphilitic process in the central nervous system, because they may persist or become more marked as a result of past activity or there may be transitory clinical improvement without a complete arrest of the syphilitic process as shown by spinal-fluid findings. Also, the syphilitic infection may be very active within the central nervous system and still be asymptomatic.

2. A positive spinal-fluid Wassermann test alone is not proof of active neurosyphilis. It merely indicates the specific nature of the infection, which may be already inhibited or completely checked at the time when the spinal fluid is examined. Activity is demonstrated only by the entire spectrum of spinal-fluid tests, among which increased cell counts and total protein determinations are of chief importance. Colloidal reactions are important but less informative than cell counts and protein determinations.

3 In treated cases, spinal-fluid Wassermann tests and colloidal reactions may continue positive for more than 5 years after treatment has successfully arrested the syphilitic process. In an arrested case, cell counts should become normal within 3 to 4 months after treatment, and quantitative complement fixation tests, protein values, and colloidal reactions should show a gradual but steady trend toward normal.

4 In cases of neurosyphilis under the older forms of prolonged specific therapy with bismuth and arsenical drugs, normal spinal-fluid cell counts and protein content merely indicate that the infectious process is inhibited if therapy is discontinued, the syphilitic process may become active again within 6 months after treatment is stopped, as shown by increased cells in the spinal fluid.

5 Following malaria therapy or penicillin therapy of active neurosyphilis, the spinal-fluid findings may show a trend toward normal values, only to relapse later Relapses, however rarely occur more than 1 year after therapy and at Bellevue Hospital we have never observed a relapse of neurosyphilis more than 15 months after treatment. If the cell count is not normal and there is no definite improvement in the other spinal-fluid findings 6 months after treatment, further treatment is imperative, regardless of the clinical status of the patient

From the foregoing summary it is obvious that the diagnosis and management of neurosyphilis depend on the results of spinal-fluid examinations. To stress this point is not to minimize the importance of clinical findings or the desire of patients to recover normal function of injured or destroyed nerve tissue. Of course the desideratum of all therapy is to achieve normal function, if that is possible, but no treatment can be evaluated on the basis of the desire to achieve the impossible. The cardiologist does not expect to replace a myocardial infarct with normal-functioning heart muscle neither can the neurologist or syphilologist restore normal function to permanently damaged nerve tissue. Arresting an active syphilitic process in the central nervous system frequently produces dramatic improvement in function, but it cannot always prevent further progress of symptoms. An old tabetic with inactive spinal-fluid findings may give the impression of progression because bladder symptoms may become worse or develop for the first time, and lightning pains may become more frequent. But such symptoms do not prove progress of the syphilitic process, and, if the spinal-fluid tests are normal or inactive, antisyphilitic treatment will rarely cause clinical improvement. Syphilitic injury of long standing in the brain, spinal cord, or posterior nerve roots leaves more or less permanent damage. The patient has a lowered central-nervous-system reserve, just as a patient with an injured heart has a lowered cardiac reserve. In the case of arrested neurosyphilis, intercurrent infections, fatigue, and a host of other factors may adversely influence the functioning of damaged nerve tissue.

For example, a patient with arrested general paresis may function fairly normally when rested and in good health, only to show signs of confusion or loss of concentration when fatigued or ill. Cystitis may increase incontinence or even cause it in the case of a cord bladder Lightning pains in patients with injured posterior nerve roots are notorious for their inconstancy and the effect which weather and many other factors have in producing them. Such symptoms are seldom if ever due to a progression of the syphilitic process in patients with inactive spinal fluids. We have verified the truth of these statements in many cases on our service. Neither malaria nor penicillin has proved effective in relieving symptoms in most cases of neurosyphilis with inactive spinal fluids. We have had a few exceptions to this rule, but they are difficult to evaluate and do not materially affect the rule.

In view of the significance of spinal-fluid examinations, this chapter might well be devoted to them alone. The variety of diseases caused by

neurosyphilis, however is of such great interest that each of the main classifications will be briefly considered.

CLASSIFICATION OF NEUROSYPHILIS

Numerous different classifications of the clinical syndromes caused by neurosyphilis can be made. For practical purposes, however the classification given by Moore in his book *Penicillin in Syphilis* seems the most satisfactory The following classification of neurosyphilis, with minor changes, is that given by Moore *

1 Asymptomatic
2. Acute syphilitic meningitis of early syphilis
3 Meningovascular syphilis, which includes arachnoiditis and all clinical syndromes which do not fit into some other recognizable classification
4 Vascular neurosyphilis which is thrombosis or hemorrhage of cerebral vessels
5 General paresis
6 Tabes dorsalis
7 Taboparesis
8. Erb s spinal spastic paraplegia
9 Syphilitic (nonparetic) epilepsy
10 Gumma of brain or spinal cord
11 Primary optic atrophy
12 Eighth-nerve deafness

ASYMPTOMATIC NEUROSYPHILIS

By definition asymptomatic neurosyphilis is diagnosed solely by means of spinal-fluid examinations. The line of demarcation between asymptomatic and symptomatic neurosyphilis is not made easily Many patients classified as having asymptomatic neurosyphilis have volunteered the information after treatment that they felt better The physical examination may have revealed no abnormal signs, but if more refined aids to diagnosis had been used, minor abnormalities might have been found.

Spinal fluid abnormalities in patients with asymptomatic neurosyphilis do not necessarily become normal any more rapidly than those of patients with symptomatic neurosyphilis. The duration of the syphilitic process is a more important factor in determining how soon abnormal

* Modified from *Penicillin in Syphilis* by J E Moore Charles C. Thomas, Publisher Springfield Ill., 1946, pp. 224–25

spinal-fluid tests become normal after treatment than the presence or absence of clinical signs and symptoms. Patients with neurosyphilis of less than 2 years duration will usually have completely normal spinal-fluid tests within 6 to 15 months after treatment. Those who have had neurosyphilis from 2 to 5 years may have completely normal spinal fluid tests within 1 to 3 years after treatment. In the case of neurosyphilis of more than 5 years' duration, whether asymptomatic or symptomatic, the time required for the Wassermann and colloidal reactions of the spinal fluid to become normal varies greatly in different individuals. The tests may become normal within 2 years in some cases, while in others low complement fixation titers and slightly abnormal colloidal tests have been found 7 years after treatment. Asymptomatic neurosyphilis is not necessarily a benign form of central-nervous-system involvement, and it should be treated as energetically as the symptomatic types.

ACUTE SYPHILITIC MENINGITIS

Acute syphilitic meningitis is a manifestation of early syphilis. It was described in Chap. 9 Immunologically it belongs in the acute phase of the disease but, if not cured, serious types of late neurosyphilis usually develop.

MENINGOVASCULAR SYPHILIS

Meningovascular syphilis is a catch-basket for all types of symptomatic neurosyphilis that do not fit definitely into other classifications.

Symptoms and signs.—The symptoms and signs depend on the sites of foci of infection in the central nervous system and the degree of damage produced. An arachnoiditis may cause blockage of the spinal-fluid circulation in some cases. Rarely a severe type of chronic meningitis develops, with large numbers of cells in the spinal fluid. The cranial nerves at the base of the brain may be injured in such cases. Pupillary changes may or may not be present. The pupils may be unequal irregular and unable to contract in strong light, or they may respond poorly to light. The Argyll Robertson pupil reacts poorly to light or is fixed to light and yet contracts extensively on convergence. It is frequently seen in cases of tabes dorsalis but is not unusual in meningovascular syphilis. The deep reflexes may be normal, or unequal reflexes may be found. Psychoses have been attributed to meningovascular syphilis, but the diagnosis in such cases is made with difficulty and usually depends on a therapeutic test.

Spinal-fluid findings.—Increased cells and positive Wassermann re

actions are found in the spinal fluid in all active cases. The total protein values may be normal or almost normal in some cases and very high in others. Colloidal reactions may be either first zone, mid zone, or end-zone in type.

Prognosis.—The prognosis following treatment depends entirely on the amount of permanent structural damage that has occurred. In many cases treatment is followed by a gain in weight and improved sense of well being, as well as relief of nervous symptoms.

VASCULAR NEUROSYPHILIS

Syphilitic involvement of the cerebral or spinal vessels without other inflammatory changes in the central nervous system is probably very rare. The small vessels are involved in all lesions of late neurosyphilis, but, occasionally thrombosis or hemorrhage may occur as a result of syphilis of one of the larger vessels. The commonest clinical manifestation of vascular neurosyphilis is hemiplegia, but vascular accidents caused by syphilitic involvement of medium-sized vessels have been found at autopsy at other sites in the central nervous system than the internal capsule of the brain. Occasionally a vascular accident resulting from syphilis of one of the vessels in the spinal cord can be suspected from the sudden appearance of signs and symptoms referable to a level in the cord.

Diagnosis.—During life, vascular syphilis in the brain and spinal cord unassociated with other forms of neurosyphilis can rarely be diagnosed with assurance, especially when the spinal-fluid findings are normal. At best, during life, the diagnosis in such a case is a guess. No one can be certain, for example, that a hemiplegia, even in a young person, is due to syphilis merely because the blood STS are positive. A hemiplegia in a syphilitic with normal spinal-fluid tests might be caused by vascular syphilis, but I have never been able to make such a diagnosis with assurance. A therapeutic test in such cases is indicated, but it does not necessarily prove the diagnosis.

GENERAL PARESIS

Prior to the introduction of malaria therapy by Wagner Jauregg, general paresis was the most malignant type of neurosyphilis. All untreated paretics died within 5 years after the onset of symptoms. The disease is due to a diffuse syphilitic involvement of the cerebral hemispheres and meninges which, if unchecked, causes marked mental deterioration and death. As noted in Chap. 2, the onset of symptoms may be gradual and insidious, or it may be sudden.

Symptoms and signs.—The earliest symptoms are frequently headache and insomnia associated with restlessness. Memory defects are usual in the early symptomatic stage but are not always easily detected. The ability to concentrate for long periods is lost. A patient may be able to multiply and divide well for 10 or 15 minutes, after which stupid errors may be made. *Dysarthria is frequent but not always present. It is best* demonstrated by asking the patient to repeat such classical test phrases as "Methodist Episcopal Church," "medical electricity" and "third riding artillery brigade." *The difficult syllables are slurred because of the poor* co-ordination of the muscles of speech. Most patients with early symptoms of general paresis are euphoric. They rarely admit disability especially mental disability and they will not even admit to headaches unless carefully questioned. The early symptoms of the disease are consequently easily missed on routine examinations of patients. In the later stages of the disease personality changes are prominent because of a more or less complete loss of the sense of responsibility. The memory defects increase until the patient lives only in the moment. Delusions of grandeur may appear and a severe form of insanity develops. The euphoric or grandiose type of personality is more frequently seen in general paresis than the melancholic and depressed type. The latter however is occasionally seen, and strong suicidal tendencies may develop in such patients.

The most characteristic signs of general paresis are perioral tremors and fine tremors of the tongue and fingers. The handwriting is frequently unsteady and may become entirely illegible. Pupillary changes may or may not be present. The deep reflexes are frequently exaggerated.

Spinal-fluid findings.—The diagnosis of general paresis is made from clinical symptoms and signs, but it cannot be made in untreated patients with normal spinal-fluid findings. The spinal-fluid Wassermann test is always positive, and increased cells and protein are always present in the spinal fluid of patients with active general paresis. Practically all cases have a first zone type of colloidal reaction, but the diagnosis does not depend on this so-called paretic type of colloidal test.

Prognosis.—Amazing improvement frequently occurs in paretics following malaria therapy or penicillin. As a rule, the prognosis is much better in the euphoric than the depressed cases. Patients with marked mental deterioration rarely recover their previous ability or sense of responsibility but they may show great improvement. Death from general paresis can be prevented in most cases with either malaria or penicillin therapy but far-advanced cases may have enough degeneration to require permanent institutional care.

Clinical evaluation of therapy.—I do not believe that the results of therapy of general paresis can be satisfactorily evaluated on a clinical basis. Remissions of the disease occur even in the absence of treatment, but the spinal-fluid tests in such cases continue to show signs of active infection. The clinical effects of antisyphilitic treatment are usually apparent within the first few months after therapy is started, after which time the patient may or may not show continued improvement. In most cases, after the initial effects of treatment have been noted, it is impossible to determine the activity of the syphilitic process by clinical observations. The lowered reserve of the brain is reflected in the moods and mental capacity of the patient during states of fatigue, illness, and emotional disturbances. As a result, the patient may seem to be markedly improved at one time and worse at another. The criterion of whether or not a treated paretic is able to hold a job is anything but reliable in evaluating the results of therapy. The variables that enter into job holding are indeed great, since they include the influence of family and friends as well as economic conditions and a host of other factors. I have known treated paretics who were euphoric and silly to hold jobs, while others who were more responsible failed to obtain employment. Following malaria therapy long courses of Tryparsamide have been given to many paretics in institutions but rarely with any demonstrable clinical benefit. Treatment designed to kill treponemes cannot replace scar tissue with functioning parenchyma. The evaluation of the results of treatment of general paresis, like that of all other forms of neurosyphilis, depends on spinal-fluid examinations.

TABES DORSALIS

Unlike the meningoencephalitis of general paresis, the degenerative changes in the posterior columns of the spinal cord in tabes dorsalis may continue for years, only to stop spontaneously without treatment. Why this should be true is one of the numerous unsolved problems of tabes dorsalis. The clinical signs and symptoms may become stationary regardless of treatment, in some cases and progress in others. Patients may live to a ripe old age even with fairly advanced locomotor ataxia. In almost every chronic-disease hospital one finds a few elderly individuals who are so markedly ataxic that they spend most of their time in a wheel chair. In other cases arrested tabes dorsalis may be found in untreated patients who have only pupillary changes and absent knee and ankle jerks. The spinal-fluid tests of arrested cases show no evidence of activity although the Wassermann reaction may still be positive.

Numerous theories regarding the pathogenesis of tabes dorsalis have been suggested, but, as previously noted, none is satisfactory. Within recent years neurologists have increasingly stressed the fact that a tabetic syndrome may have other causes than syphilis. Wilson, Guttman, Herman, Dattner and others have reported cases of Argyll Robertson pupils and absent knee and ankle jerks that were not due to syphilis.

Adie's syndrome, which is never due to syphilis, consists of tonic pupils associated with absent knee jerks and ankle jerks. The pupillary changes in Adie's syndrome are not those of an Argyll Robertson pupil. The pupil is not fixed to light but contracts so slowly to light and on convergence that it may appear to be fixed unless the light is flashed into the eye for some time. After the pupil has contracted, it requires an even longer time for it to dilate. It may even be necessary to place the patient in a dark room to observe the dilatation after the pupil has contracted.

Symptoms and signs.—The symptoms and signs of tabes dorsalis are readily traced to their source in the posterior columns of the spinal cord, posterior nerve roots, and ganglia. The Argyll Robertson pupil is in no *way diagnostic of tabes dorsalis, but it occurs more frequently in tabes* than in other forms of neurosyphilis. The tendon reflexes of the lower extremities (ankle and knee jerks) are usually absent, and in occasional cases where the degenerative process extends up to the thoracic portion of the spinal cord, all deep reflexes may be lost. Paresthesias of the skin may occur. Hypotonia of the muscles is usual. Position and vibratory sense are frequently impaired. All degrees of ataxia may be seen. Lightning pains, believed to be due to injury of the posterior nerve roots, may occur almost anywhere in the body but they are usually limited to the lower extremities. Gastric crises may develop because of injury to either the sympathetic or parasympathetic fibers. The crises consist of severe abdominal pain which may simulate an acute surgical abdomen, and, in some cases, of severe vomiting. The attacks may last for hours and sometimes for days. I vividly recall seeing two tabetics in the emergency ward of Bellevue Hospital on the same day. One had a ruptured gastric ulcer *with no pain and an absolutely flaccid* abdominal wall, while the other had a gastric crisis with a rigid abdominal wall and severe pain. The former case was diagnosed as an acute abdomen because of signs of fluid in the peritoneal cavity.

In addition to gastric crises there may be urethral crises and anal crises. Ulcers, especially of the toes, heels and soles, and Charcot's joints are the principal trophic changes that occur although the atonic cord bladder may also be included among the trophic disorders. Incontinence often results

from atony of the bladder and cystitis is common in such a bladder The libido may be diminished or lost entirely in tabes dorsalis.

Spinal-fluid findings.—In so-called burned-out tabes dorsalis, the spinal-fluid tests are all normal, and the diagnosis is made solely by history and physical findings. In spontaneously arrested cases the only abnormal spinal-fluid test may be a positive Wassermann reaction. In active cases, increased cells are present in the spinal fluid, and usually increased protein is also found. The colloidal reactions may be first zone or mid-zone in type. The quantitative complement fixation titers of the spinal fluid in active tabes dorsalis may be very low or very high. There is no relationship between the amount of reagin in the blood and spinal fluid and the activity or severity of the disease.

Prognosis.—If the spinal-fluid examination shows an active process and the symptoms are recent, antisyphilitic treatment of tabes dorsalis may be followed by definite clinical improvement. I well remember a patient whom I saw in 1937 who had a fairly sudden onset of ataxia. Within 6 weeks he had become so ataxic that he had to use crutches. He had a very "active spinal fluid," Argyll Robertson pupils, and absent knee and ankle jerks. To my amazement his ataxia began to improve after beginning therapy with bismuth, and he improved still more rapidly after arsenoxide therapy was given. He walked without a cane or crutches within 3 months and refused the fever therapy which I had advised but continued to receive arsenicals and bismuth for 2 years. Today he drives a car and has very little disability

A case such as this, with sudden onset of ataxia and rapid recovery is very rare. In most instances further progress of the syphilitic process can be checked, but it is impossible to restore normal function The ataxia usually persists, and I have never seen absent deep reflexes restored to normal by any type of antisyphilitic therapy The dramatic improvement frequently seen in general paresis after treatment is rarely observed in tabes dorsalis. The most that can be expected, as a rule, is that the symptoms and signs will become no worse, although patients frequently have an improved sense of well-being after therapy Because of the variations in the sense of well-being and the symptoms of patients following treatment for tabes dorsalis, it is extraordinarily difficult to evaluate therapy on the basis of clinical symptoms and signs alone. In our experience at Bellevue Hospital, penicillin has proved as effective as any type of fever therapy in producing clinical improvement in tabetics.

Nonspecific therapy—The treatment of tabes dorsalis does not necessarily end with antisyphilitic therapy The sequelae of th ctive disease

frequently require medical and sometimes surgical attention. The most frequent symptoms demanding treatment are lightning pains.

Treatment of lightning pains.—The sharp, shooting, neuritic pains associated with tabes dorsalis present a most annoying and puzzling problem in the care of patients who no longer have an active syphilitic process in the posterior nerve roots. Lightning pains may disappear for months, only to return in severe form for reasons which oftentimes cannot be determined. Low barometric pressure, infections, and emotional stresses are among the known inciters of lightning pains, but there are many unknown factors. In some cases relief can only be obtained with morphine, which is always undesirable because of the danger of addiction. Demerol helps at times but is not as effective as morphine. Most analgesics have little demonstrable effect on the pains.

The power of suggestion is very important in the treatment of lightning pains. It is unwise to tell tabetics that bad weather will increase lightning pains, because the mere fear or anticipation of the pains may make them worse or bring them on. Patients have told me that they were relieved of lightning pains by injections of saline as regularly as by injections of thiamine chloride. In the occasional case any placebo seems to benefit temporarily. Injections of crude liver extract several times a week have proved valuable in numerous cases of lightning pains on our service. Recently very favorable reports have been made regarding the effectiveness of a proteolytic enzyme marketed under the trade name of Protamide. I have found this preparation helpful in a few cases where it was used.

A nihilistic attitude regarding the relief of lightning pains should always be avoided, and the patient should be encouraged as much as possible. Unfortunately intractable cases are occasionally encountered. To use morphine in such cases usually leads to addiction. I have not tried procaine hydrochloride intravenously for the relief of lightning pains, but it might well be tried. Prefrontal lobotomy has been resorted to in recent years, with some favorable results. Freeman and Watts in a recent report on prefrontal lobotomy state that this procedure "does not interfere with the perception of pain, but rather with the evaluation of pain. It does not relieve the pain, but rather the disabling reaction to pain, the fear of pain. It does so apparently by eliminating the emotional component arising from the thalamus." * If other treatment can be used to good effect, obviously it should be thoroughly tried before resorting to a pre-

* Freeman, W., and Watts, J. W.: "Pain Mechanisms and the Frontal Lobes: A Study of Prefrontal Lobotomy for Intractable Pain," Ann. Int. Med., 28: 747, 1948.

frontal lobotomy but that operation is probably preferable to morphine addiction

Nonspecific therapy of other tabetic disabilities.—Ataxic patients can often be educated to improve their gait, and in certain cases mechanical aids to walking can be provided. Charcot's joints fall into the province of the orthopedists, and cord bladders require the care of the urologist. Above all, the mental and emotional states of the severe tabetic need to be treated intelligently Maloney in an excellently written and interesting book on *Locomotor Ataxia*, has shown how the symptoms of tabes dorsalis differ in the same patient at various times, depending on the degree of mental and emotional fatigue as well as on environmental, biologic, and nutritional conditions. Antisyphilitic treatment can bring little benefit to such patients unless the syphilitic process is still active. The latter can only be determined by spinal fluid examination.

TABOPARESIS

As the name implies, taboparesis is a combination of general paresis and tabes dorsalis. The diagnosis is made by finding symptoms and signs of both diseases. In past years some observers have claimed that taboparesis had a worse prognosis than either general paresis alone or tabes dorsalis alone, but, as with all neurosyphilitic diseases, the prognosis depends on the amount of permanent damage that has occurred prior to treatment. The syphilitic process can usually be arrested by malaria or penicillin therapy

SYPHILITIC SPINAL SPASTIC PARAPLEGIA

Erb's spastic paraplegia is due to degenerative changes in the lateral pyramidal tracts. It is much less common than tabes dorsalis but is not especially rare. Not all cases of spinal spastic paraplegia are caused by syphilis, but some unquestionably are. In some cases of syphilis the true etiology of spastic paraplegia is uncertain, but antisyphilitic therapy should be tried.

Symptoms and signs.—The chief symptoms are a spastic gait The signs are those of pyramidal tract disease hyperactive deep reflexes, with or without clonus, and positive Babinski's sign.

Prognosis.—In long-standing cases the prognosis is poor If a spastic gait is already present, antisyphilitic treatment rarely causes improvement, but further progress of the disease can usually be prevented. Like tabes dorsalis, spastic paraplegia may become stationary spontaneously As a rule, the chances of clinical improvement with specific treatment are

greater in patients with "active spinal fluid" than in those with "inactive spinal fluid" The effect of antisyphilitic treatment depends on the degree of degeneration of the pyramidal tracts.

SYPHILITIC (NONPARETIC) EPILEPSY

Attacks of either petit mal or grand mal may develop in the course of neurosyphilis. In the late stages of general paresis, convulsions may be frequent, but typical epileptic seizures are also occasionally noted in cases of neurosyphilis that are not associated with general paresis. The etiology of the attacks in such cases is not readily determined. The few patients with probable syphilitic epilepsy whom I have seen, with one or two exceptions, failed to be relieved of their epileptic attacks by malaria therapy or penicillin. The attacks were controlled by such drugs as Dilantin, Tridione, and phenobarbital. The neurosyphilis, if active, should, of course, be treated in the same way as all other types of active neurosyphilis.

GUMMA OF THE BRAIN AND SPINAL CORD

Gummas in the brain and spinal cord may be miliary or of large size. A diffuse distribution of miliary gummas in the brain gives symptoms of an encephalitis. I have never seen such a case, but a few have been reported at post-mortem examinations. According to Stokes, diffuse gummatous infiltration may occur but by far the commonest manifestation is that of solitary gumma which gives symptoms and signs of a tumor A fairly large gumma of the brain causes papilledema. Other signs depend on the site of the gumma in the brain. I know of two cases of gumma of the brain that came to autopsy at Bellevue Hospital without the diagnosis having been suspected, largely because of the absence of papilledema. Solitary gumma of the cord has been reported but is rare.

When definite signs of a brain or cord tumor are present, operation is preferred to waiting for the results of antisyphilitic therapy

PRIMARY OPTIC ATROPHY

Primary optic atrophy is most frequently associated with tabes dorsalis, but it may also occur in patients with meningovascular syphilis and general paresis. Neurosyphilis is the commonest, but not the only cause of primary optic atrophy

Diagnosis.—Active progressive cases of primary optic atrophy are rarely if ever due to syphilis if the patient has a completely normal spinal fluid. I have seen patients treated for syphilitic primary optic atrophy

merely because of positive STS, and at a later period it became clear that the nerve injury was due to other causes than syphilis.

Glaucoma can produce a picture similar to primary optic atrophy as can thrombosis of the blood vessels in the optic nerve. Rarely sensitivity to tobacco in heavy smokers has caused optic atrophy Kestenbaum has given an excellent differential diagnosis of optic atrophy in a recent book, *Clinical Methods of Neuro-Ophthalmologic Examination*. In spite of the variety of conditions that may cause optic atrophy the presence of white disks, *constricted peripheral fields, or central scotoma in a patient with* active neurosyphilis is always cause for energetic treatment with penicillin and/or fever therapy

Signs.—Kestenbaum describes syphilitic primary optic atrophy as follows "The disk is white the spots of the lamina cribrosa are distinctly visible in an advanced stage, a total but very flat excavation (atrophic cupping) develops the larger arteries and veins have their normal caliber except in very advanced cases when the arteries may be slightly thin the small vessels, in contrast to the larger ones, are decreased in number" * According to Kestenbaum the pallor of the disk is not an expression of atrophy of the nerve fibers but is due to disappearance of blood filled capillaries. The degree of pallor of the disk does not necessarily run parallel with the loss of vision. Two forms of primary syphilitic optic atrophy are described: (1) the typical form with constriction of the peripheral fields caused by wedge-shaped defects of the periphery of the field resulting from involvement of separate nerve bundles, and (2) atypical or central form which has a central scotoma instead of the wedge shaped peripheral defects. The appearance of the disk is similar in both, but the peripheral fields are, of course, quite different. In the first form central vision is good until the atrophy is far advanced, while in the second form the central vision may be lost entirely Kestenbaum states that the second form has a better prognosis, as a rule, than the first, and he believes that the central scotoma in the second form is the result of a retrobulbar neuritis on a syphilitic basis.

Pathogenesis.—To me the most interesting observation made by Kestenbaum in his description of syphilitic primary optic atrophy is the decrease in the number of small vessels that can be counted. This observation suggests that the degenerative changes in the nerve bundles are caused by a defective blood supply There is no pathologic proof of a syphilitic endarteritis in sections of the optic nerves in cases of syphilitic

* Kestenbaum, Alfred *Clinical Methods of Neuro-Ophthalmologic Examination* Grune & Stratton, Inc., New York, 1946.

primary optic atrophy but the obliteration of the small nutrient vessels, observed by Kestenbaum, is the most attractive explanation of the atrophy that I have found. Most pathologists, however offer no explanation of the pathogenesis of primary optic atrophy In an excellent review of the pathogenesis of syphilitic primary optic atrophy published in 1940 Moore and Woods concluded that no hypothesis regarding the mechanism of the degenerative changes was entirely satisfactory

Spontaneous arrest.—Like tabes dorsalis and spinal spastic paraplegia, primary optic atrophy occasionally is arrested spontaneously and remains stationary without antisyphilitic treatment. I have seen unquestioned examples of such spontaneous arrest. In most cases, however the process progresses and causes complete blindness, if unchecked by treatment.

Prognosis.—Either malaria therapy or penicillin will usually check further degeneration of the optic nerves in primary optic atrophy But, *occasionally in rapidly progressive cases where the condition is already* far advanced, blindness may occur in spite of treatment. In my opinion, rapidly progressive cases should be started on penicillin treatment at once, because of its quick action. If malaria therapy is given to such patients, there is an unavoidable delay of several weeks before the treatment is effective.

I have rarely observed marked improvement in the visual fields of patients with optic atrophy following either malaria therapy or penicillin, but, with few exceptions, our cases have become stationary after treatment If the disease is treated early in its course, actual improvement of vision may occur as a result of the treatment. We have found that optic atrophy in patients who have inactive spinal fluids (normal cell counts and protein) are usually stationary cases, and little can be expected from either fever therapy or penicillin in such cases unless a relapse occurs in which case the spinal-fluid tests will show increased values from previous levels. If the vision becomes progressively worse after penicillin, fever therapy should, of course, be tried.

EIGHTH NERVE DEAFNESS

Eighth-nerve deafness is usually due to involvement of the nerve by a syphilitic meningitis. It may occur in early acute syphilitic meningitis or in the late forms of meningovascular neurosyphilis. Rarely a degenerative process of the eighth nerve, similar to that of primary optic atrophy may occur The prognosis in such cases depends entirely on the amount of permanent damage to the nerve prior to antisyphilitic treatment. The treatment is that of neurosyphilis in general.

TREATMENT OF NEUROSYPHILIS

All reports on penicillin treatment of neurosyphilis agree that there has been a satisfactory response of the spinal-fluid findings in a very high percentage of cases following treatment. Up to the present, however there has been a difference of opinion regarding the comparative effects of malaria therapy and penicillin from the point of view of clinical improvement.

O'Leary Solomon, Rose, Leavitt, and Heyman have advised malaria therapy in addition to penicillin in cases of general paresis. The articles which have been published by them, however were in most cases written during the first 2 years of the investigation of penicillin therapy and it may be that further experience will alter some of their early impressions. It is not surprising that malaria therapy should be preferred to penicillin until the latter has proved itself beyond any doubt. Both Dattner and I were originally skeptical that penicillin would prove equal to malaria therapy in the treatment of general paresis.

In the past year there has been a steadily increasing number of authors who report that penicillin is at least equal to if not better than, malaria therapy in the treatment of all types of neurosyphilis including general paresis. Some of the most striking reports have come from England. Nicol, who has been affiliated with the Malaria Therapy Center in Horton, England, for many years, states "One of the most striking clinical features [of penicillin therapy in general paresis] was the physical and mental improvement in many patients. Most dramatic results were seen in patients who were confused and in poor physical condition." Martin, in a recent article in the *British Medical Journal*, also praises penicillin and expresses his surprise at the clinical improvement as well as the improvement in spinal-fluid findings of patients treated for neurosyphilis with penicillin. He says that the treatment of neurosyphilis is "penicillin plus time," and he believes that the spinal fluid examination is the best guide to the results of therapy Among the American authors who have found penicillin the equal of malaria therapy are Dattner Callaway Curtis, Crawford, Gilpin, Jones and Perk, and Parkhurst and Bowman.

RESULTS OF PENICILLIN THERAPY OF NEUROSYPHILIS AT BELLEVUE HOSPITAL

The following report is taken largely from Dattner's most recent

Nicol, W D Penicillin in General Paresis, *Brit. M J* 1 734 (May 24) 1947

evaluation of the results of penicillin treatment of neurosyphilis on our service at Bellevue Hospital

Over 400 patients with various forms of neurosyphilis were treated with penicillin since April, 1944 Of this number the report includes only 376 patients who had "active spinal fluids" with pleocytosis and increased total protein values. Of the 376 patients, 67 were lost and 8 were known to have died since their treatment. The remaining 301 were observed over a period of 6 months to 4 years 10 per cent were under observation for more than 3 years, 35 per cent for more than 2 years, and 70 per cent for more than 1 year The longest observation period was 45 months. The only antisyphilitic treatment used was penicillin. The total dosage varied from 2,000 000 to 9 000 000 units, and the number of injections from 75 to 200 All patients in this series received aqueous solutions of penicillin individual injections having been given every 3 hours. The treatment failures following the first course of penicillin as indicated by relapse of spinal-fluid findings or continued pleocytosis, are shown in Fig 62. From this table it will be seen that the highest percentage of

FIG. 62. FAILURE OF PATIENTS FOLLOWING FIRST COURSE OF PENICILLIN TREATMENT

Diagnosis	Number of Patients	Failures	Successful Re-treatment
Asymptomatic	61	8	6
Meningovascular	75	13	7
Tabes dorsalis	83	7	2
Dementia paralytica	53	6	4
Taboparesis	29	0	0
	301	34	19

failures following the first treatment occurred in the group classified as having meningovascular syphilis, and the next highest percentage of failures occurred in the asymptomatic group The relatively large number of re-treatments in these two groups can be explained by the fact that, for the most part, they received total doses of less than 4 000 000 units of penicillin. The patients with general paresis and taboparesis received at least 4 000 000 units, and the majority had 6 000 000 units. In the entire series 34 or 11.2 per cent, were re-treated.

Of the 34 patients in all groups who were re treated 19 responded

satisfactorily to a second course of treatment with larger doses of penicillin, and 14 had not yet been followed a sufficient time for evaluation. 1 relapsed *a second time and was treated a third time with 15,000,000* units of penicillin in 25 days. We do not yet know the results of the third treatment of this patient. He was always asymptomatic, and he never achieved a normal cell count in the spinal fluid. After each of the first two treatments the spinal-fluid tests improved but later relapsed. This patient may require malaria therapy, but, so far, he is the only complete failure in the entire series treated with penicillin.

Even if the underdetermined group of 15 re-treated patients (only 1 of whom has relapsed following a second treatment) were classified as unsuccessful, the percentage of definite successes would be 96, and in all probability the percentage of ultimately satisfactory results, based on spinal-fluid findings, will be close to 100. With one exception, satisfactory responses of the spinal-fluid tests occurred in the 8 patients who died since penicillin treatment; only one death could possibly be attributed directly to neurosyphilis.

Of the 301 patients in the penicillin series, 31 had optic atrophy: 3 were blind when treatment was started; 1 had no vision in one eye and only light perception in the other; 6 had only light perception in both eyes; the remaining 21 had constricted peripheral fields or central scotoma. Some progressive loss of vision following treatment was noted in 3 cases only.

Results such as these are surprisingly good and even better than those obtained with malaria therapy. Among the patients who were treated with penicillin were 5 who had had one or more previous treatments with malaria therapy and many injections of bismuth and arsenicals. The chart of one of these patients is shown in Fig. 63.

It is, of course, admitted that the degree of clinical improvement noted in the symptomatic cases was not always comparable to the improvement noted in the spinal-fluid findings. This was anticipated for reasons which have been given in previous discussions. Nevertheless, the clinical improvement was certainly comparable to that observed in previous years following malaria therapy. From January, 1939, to April, 1944, all of our patients with active neurosyphilis received malaria therapy. During those years we were never without quartan and tertian malaria in our wards. In addition, Dattner had treated and followed up for many years large series of patients treated with malaria in Wagner Jauregg's clinic in Vienna. Consequently, in spite of the difficulty of comparing the clinical

FIG. 65. RE-TREATMENT OF PATIENT WITH INACTIVE SPINAL FLUID PATIENT FIRST TREATED FOR ACTIVE TABES DORSALIS WITH 3,000,000 UNITS OF PENICILLIN MAY 30, 1944 TO JUNE 18, 1944

DATE	S. WASS.	CELLS	ANDY	TOTAL PROTEIN	COLLOIDAL GOLD
5/24/44	4+ in 0 1 cc	276/3	3+	83	4552210000†
8 12 44	4+ in 0 1 cc	11/3	1+	44	1111000000
10 14 44	69*	4/3	+	40	17 16,16,16,16,15 13,9 7,5(130)‡
1 13 45	62	3 3	2+	43	15 16,17 17 16,14,9.5 7.5,5,5.5(120)
3 23 45	49	3/3	V F T	37	16,17 18,18,15 14,8.5 7.5,5.5(122)
7 16 45	54	7/3	V T	45	12,15 17 18,17 16,11,8,6.5(125)
10 27 45	47	14 3	±	37	14 16,16,17 15,9,8,6.5,2.5(109)
1 15 46	4	4/3	F T	36	16,16,16,17 17 16,9 7 6,3.5(124)
3 10 46	34	9/3	V F T	33	15 16,16,17 16,15 12,9 6,4(126)

RE-TREATED WITH 6,000,000 UNITS OF PENICILLIN IN SEPTEMBER, 1946

TE	WAS	CELL	ANDY	TOTAL PROTEIN	COLLOIDAL GOLD
9/ 5 46	26	6 3	F T	29	15 16,16,16,15,8.5,8.5,5.5 4.5 2(107)
12 24 46	78	2 3	F T	33	12,16,17 16,13,8,6.5,5,2,2.5(98)
5 15 47	17	3	V F T	29	16,16,14 12,11,8.5 7 4,3.5,2.5(95)
11 7 47	27	3 3	±	29	7.5 11 11 13 12,11,8.5 7.5,5,3.5(90)
4 26 48	23	3 3	V F T	31	9 13 12,12,12,11 7.5 7,5.5,3.5(93)

Titrated in units.
† Old Lange colloidal gold technique.
‡ New Lange colloidal gold technique. (Total of 10 readings should not be over 45)

improvement in different series of patients treated at different times, we do not lack an extensive experience with malaria therapy for comparison with penicillin treatment.

In 1943 Dattner Wexler and I reported the results of malaria treatment of 419 patients with active neurosyphilis observed from 6 months to 4 years. The percentage of satisfactory results in the entire series was about 85 Many of these patients have now been followed for 8 years or more. In the majority of cases the spinal-fluid findings became normal within 5 years, but a few still have slightly abnormal colloidal tests and low Wassermann titers more than 7 years after treatment. The spinal-fluid reports of one of these cases are shown in Fig 64

Once the spinal fluid has become inactive and remains inactive, re-treatment will not hasten the rate at which Wassermann and colloidal reactions become normal. An example of this observation is shown in Fig 65

The rate at which the spinal-fluid Wassermann and colloidal reactions become normal after the spinal fluid has become inactive has no relationship to the severity of the clinical manifestations. A deteriorated paretic or dilapidated tabetic may obtain a normal spinal fluid after treatment more rapidly than may an asymptomatic patient, and vice versa.

Because of the possibility of relapses following therapy spinal-fluid examinations should be repeated every 3 to 4 months during the first year Relapses rarely occur after 1 year and it is usually safe to examine the spinal fluid at 6-month intervals during the second year after which time, if it is difficult to obtain the spinal fluid, yearly tests should suffice.

Attention is called to the fact that neurosyphilitics who have had recent treatment with bismuth and arsenicals may have inactive spinal fluids which are very likely to show evidences of renewed activity within 6 months after the treatment is stopped. The results of bismuth and arsenical therapy of neurosyphilis are, in general, poor

TREATMENT SCHEDULES

Active neurosyphilis should be treated with at least 6 000 000 units of penicillin over a period of not less than 15 days, and preferably 21 days. The slowly absorbed preparations of penicillin can be used as suggested in Chap. 7 but as yet the results of therapy with the aluminum monostearate preparations are unknown So far daily injections of 600,000 units of POB have given good results in the treatment of all types of neurosyphilis at Bellevue Hospital. It must be recognized that penicillin preparations that are very [illegible]bed do not give as high blood con

evaluation of the results of penicillin treatment of neurosyphilis on our service at Bellevue Hospital.

Over 400 patients with various forms of neurosyphilis were treated with penicillin since April, 1944 Of this number the report includes only 376 patients who had "active spinal fluids" with pleocytosis and increased total protein values. Of the 376 patients, 67 were lost and 8 were known to have died since their treatment. The remaining 301 were observed over a period of 6 months to 4 years 10 per cent were under observation for more than 3 years, 35 per cent for more than 2 years, and 70 per cent for more than 1 year The longest observation period was 45 months. The only antisyphilitic treatment used was penicillin. The total dosage varied from 2 000 000 to 9 000 000 units, and the number of injections from 75 to 200 All patients in this series received aqueous solutions of penicillin, individual injections having been given every 3 hours. The treatment failures following the first course of penicillin, as indicated by relapse of spinal-fluid findings or continued pleocytosis, are shown in Fig 62 From this table it will be seen that the highest percentage of

FIG. 62. FAILURE OF PATIENTS FOLLOWING FIRST COURSE OF PENICILLIN TREATMENT

DIAGNOSIS	NUMBER OF PATIENTS	FAILURE	SUCCESSFULLY RE-TREATED
Asymptomatic	61	6	6
Meningovascular	75	15	7
Tabes dorsalis	83	7	2
Dementia paralytica	53	6	4
Taboparesis	29	0	0
	301	34	19

failures following the first treatment occurred in the group classified as having meningovascular syphilis, and the next highest percentage of *failures occurred in the asymptomatic group The relatively large number* of re-treatments in these two groups can be explained by the fact that, for the most part, they received total doses of less than 4 000 000 units of penicillin The patients with general paresis and taboparesis received at least 4 000 000 units, and the majority had 6 000,000 units. In the entire series 34 or 11 2 per cent, were re-treated.

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satisfactorily to a second course of treatment with larger doses of penicillin, and 14 had not yet been followed a sufficient time for evaluation 1 relapsed a second time and was treated a third time with 15 000,000 units of penicillin in 25 days. We do not yet know the results of the third treatment of this patient. He was always asymptomatic, and he never achieved a normal cell count in the spinal fluid. After each of the first two treatments the spinal-fluid tests improved but later relapsed. This patient may require malaria therapy but, so far he is the only complete failure in the entire series treated with penicillin.

Even if the undertermined group of 15 re-treated patients (only 1 of whom has relapsed following a second treatment) were classified as unsuccessful, the percentage of definite successes would be 96 and in all probability the percentage of ultimately satisfactory results, based on spinal-fluid findings, will be close to 100 With one exception, satisfactory responses of the spinal-fluid tests occurred in the 8 patients who died since penicillin treatment only one death could possibly be attributed directly to neurosyphilis.

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Results such as these are surprisingly good and even better than those obtained with malaria therapy Among the patients who were treated with penicillin were 5 who had had one or more previous treatments with malaria therapy and many injections of bismuth and arsenicals. The chart of one of these patients is shown in Fig 63

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FIG. 63. PENICILLIN SUCCESS AFTER FAILURE OF TREATMENT WITH TRIVALENT ARSENICALS, BISMUTH, MALARIA THERAPY AND PENTAVALENT ARSENICALS

R.S. Age 41 — White Male — General Paresis

Patient received 30 arsenicals and 80 bismuth injections from April 30, 1937 to January 15 1941 He had eight fevers from induced quartan malaria from September 23 1941 to November ., 1941 followed by 10 daily injections of 0.06 gm mapharsen. He then received 72 injections of pentavalent arsenicals from December 4 1942, to December 29 1944

DATE	BLOOD WASS.	F WASS.	CELLS	PANDY	TOTAL PROTEIN	COLLOIDAL GOLD
9 9 41	4+	4+ in 0 1 cc	250/3	3+	32	5544321000†
5 19 42	4+	4+ i 0.1 cc	270/3	3+	30	5544321000
11 30 42	4+	4+ in 0.1 cc	200/3	3+	32	3332100000
4 10 44	4+	4+ in 0.1 cc	130/3	4+	34	1111000000
1 15 45	35	45	168/3	Neg.	29	106‡

January 30, 1945, to February 15 1945—5 000,000 units of penicillin

DATE	BLOOD W R.	S. WASS.	CELLS	PANDY	TOTAL PROTEIN	COLLOIDAL GOLD
2 15 45	22	29	29/3	V F T	24	74
6 20 45	6	7	8/3	Neg.	37	74
10 15 45	3	7	2/3	V.F T	25	52
3 25 46	3	2	3/3	±	21	52
9 27 46	3	Neg.	3/3	Neg.	21	50
3 3 47	2	2	2/3	Neg.	19	44
1 8 47	2	Neg.	4/3	Neg.	22	40
6 25 48	2	Neg.	2/3	Neg	19	36

Titrated in units.
† Old Lange colloidal gold technique.
‡ The figures represent the sum of readings in all 10 tubes by new Lange method. (Normal is 45 or less.)

FIG. 64. SPINAL-FLUID REPORTS OF PATIENT TREATED FOR GENERAL PARESIS WITH MALARIA FOLLOWED BY 10 DAILY INJECTIONS OF 0.06 GM MAPHARSEN NOVEMBER 29 1939 TO DECEMBER 15, 1939

DATE	WASS.	CELLS	ANDY	TOTAL PROTEIN	COLLOIDAL GOLD
11/14/39	4+ in 0 1 cc	226/3	4+	71	5554320000†
1 19 40	4+ in 0 1 cc	30/3	2+	60	4332000000
10 15 40	4+ in 0.1 cc	2/3	1+	28	2111000000
4 21 41	4+ in 0.1 cc	4/3	Neg.	20	0000000000
10 20 41	4+ in 0.1 cc	3/3	Neg.	21	0000000000
10 15 42	1+ in 0.1 cc	1/3	F T	28	0000000000
3 20 47	6	0	Neg.	21	5.5 7 7.5,9,8,7,5.5 4,2.5,2(58)‡
5 10 48	3	1/3	Neg.	16	7,8,8.5,8.5 7.5 7.5 6,4.5,3.5 1.5(63)

Titrated in units.

† Old Lange colloidal gold technique.

‡ New Lange colloidal gold technique. (Total of 10 readings should not be over 45) Note how much more sensitive the new Lange colloidal gold curve is than the older one.

FIG. 63. RE-TREATMENT OF PATIENT WITH INACTIVE SPINAL FLUID. PATIENT FIRST TREATED FOR ACTIVE TABES DORSALIS WITH 3,000,000 UNITS OF PENICILLIN MAY 30, 1944 TO JUNE 18, 1944

DATE	F W	CELLS	PANDY	TOTAL PROTEIN	COLLOIDAL GOLD
5/24/44	4+ in 0.1 cc	276/3	3+	83	4552210000†
8/12/44	4+ in 0.1 cc	11/3	1+	44	1111000000
10/14/44	69*	4/3	+	40	17 16,16,16,16,15 11,9 7,5(130)‡
1/13/45	62	3/3	+	43	15 16,17 17 16,11,9.5 7.5,5,3.5(120)
3/29/45	49	3/3	V.F.T	37	16,17 18,18,15 14 8.5 7.5,5,3(122)
7/16/45	54	7/3	V.T	45	12 13 17 18,17 16,11,8,6.5(125)
10/27/45	47	14/3	±	37	14 16,16,17 15,9,8,6.5,2.5(109)
1/15/46	42	4/3	F.T	36	16,16,16,17 17 16,9 7 6,3.5(124)
5/10/46	31	9/3	V.F.T	35	15 16,16,17 16,15 1_9 6,4(126)

RE-TREATED WITH 6,000,000 UNITS OF PENICILLIN IN SEPTEMBER, 1948

DATE	W	CELLS	PANDY	TOTAL PROTEIN	COLLOIDAL GOLD
9/5/46	26	6/3	F.T	29	15 16,16,16,15,8.5,8.5,5.5 4.5,2(107)
12/24/46	28	2/3	F.T	33	12,16,17 16,13,8,6.5,5,2,2.5(98)
5/15/47	17	2/3	V.F.T	29	16,16,14 12,11,8.5 7 4,3.5,2.5(95)
11/7/47	27	5/3	±	29	7.5 11 11 13,12,11,8.5 7.5,5,3.5(90)
1/26/48	23	3/3	V.F.T	31	9 13 12,12,12,11 7.5 7.5,5,3.5(93)

*Titrated in units.
† Old Lange colloidal gold technique.
‡ New Lange colloidal gold technique. (Total of 10 readings should not be over 45.)

improvement in different series of patients treated at different times, we do not lack an extensive experience with malaria therapy for comparison with penicillin treatment.

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Attention is called to the fact that neurosyphilitics who have had recent treatment with bismuth and arsenicals may have inactive spinal fluids which are very likely to show evidences of renewed activity within 6 months after the treatment is stopped. The results of bismuth and arsenical therapy of neurosyphilis are, in general, poor

TREATMENT SCHEDULES

Active neurosyphilis should be *treated with at least 6 000,000 units of* penicillin over a period of not less than 15 days, and preferably 21 days. The slowly absorbed preparations of penicillin can be used as suggested in Chap. 7 but as yet the results of therapy with the aluminum monostearate preparations are unknown. So far daily injections of 600,000 units of POB have given good results in the treatment of all types of neurosyphilis at Bellevue Hospital. It must be recognized that penicillin preparations that are very slowly absorbed do not give as high blood con

centrations as more rapidly absorbed preparations. Further experience in the treatment of neurosyphilis with penicillin and aluminum monostearate may show that these preparations do not yield sufficiently high blood concentrations for optimum therapy

REFERENCES

Alpers B. J "Vertigo as the Presenting and Only Symptom of Neurosyphilis," *Am J Syph. Gonor & Ven Dis* 31 322, 1947

Callaway J L. Noojin R. O Flower, A. H., Jr. Kuhn B H. and Riley K. A. "The Use of Penicillin in the Treatment of Syphilis of the Central Nervous System, *Am. J Syph. Gonor & Ven. Dis.* 30 110 1946.

Costello R. T "A New Treatment for the Lighting Pains of Tabes Dorsalis," *Urol. & Cutan Rev* 51 260 1947

Crawford G M Medical Progress Syphilis, *New England J Med* 236 280 1947

Dattner, B. *Management of Neurosyphilis*, Grune & Stratton, Inc., New York, 1944

——— "Neurosyphilis and the Latest Methods of Treatment, *M Clin. North America* 32 707 1948

——— and Thomas E. W "The Management of Neurosyphilis," *Am. J Syph., G nor & Ven Dis* 26 21 1942.

——— ——— and Wexler, G Rapid Treatment of Neurosyphilis with Malaria and Chemotherapy" *Am. J Syph G nor & Ven. Dis.* 28 265 1944

Delay M. J Dreyfus-Moreau J and Stevenin L. "Action de la penicilline dans une paralyse générale juvenile *Ann. méd psych* l 104 152, 1946.

Freeman W and Watts, J W Pain Mechanisms and the Frontal Lobes A Study of Prefrontal Lobotomy for Intractable Pain, *Ann. Int M d* 28 747 1948.

Gammon G D Stokes J H. Steiger, H. P Steele, W H. Brenman H. Ingraham N R., Jr. Gyorgy P Rose, E. Lentz J W Ornstein A. and Scott D Penicillin Therapy Alone in Neurosyphilis, *Ann Int M d* 25 412 1946.

Gilpin S F "Neurosyphilis," *Progress of Neu ol. & Psychiat* Vol. 2 Grune and Stratton, Inc., New York, 1947 p. 282.

Heyman A. "Treatment of Syphilis of the Central Nervous System with Penicillin," *Am. J M Sc* 213 661 1947

Jones W L. and Perk, D "The Early Results of Penicill n Treatment in General Paresis, *J Ment Sc* 92 414 1946

Kestenbaum A. *Clinical Methods of Neuro-Ophthalmologic Examination* Grune & Stratton, Inc., New York, 1946.

Koteen H. Doty E. J Webster, B. and McDermott W Penicillin

Therapy in Neurosyphilis," *Am. J Syph. Gonor & Ven. Dis.* 31 1 1947

LANGE, C. "Interpretation of Findings in the Cerebrospinal Fluid. I. The Dementia Paralytica Formula and the Necessity of Its Quantitative Differentiation," *Arch Neurol & Psychiat.*, 53 116 1945

——— and HARRIS A. H. A Citrate Gold of Optimal and Reproducible Sensitivity for Use in the Colloidal Gold Reaction. Its Preparation and Control, *Am. J Pub Health* 34 1087 1944

——— and ——— "The Significance of the *p*H in the Gold Reaction," *J Lab & Clin. M d.*, 29 970 1944

LEAVITT H. M. "Neurosyphilis, *Arch. Dermat & Syph.* 56 233 1947

MALONEY W J M. A *Locomotor Ataxia Tabes D rsalis* D Appleton-Century Company Inc., New York, 1918.

MARTIN J P "The Treatment of Neurosyphilis with Penicillin," *Brit M J* 1 922, 1948.

MERRITT H. H. ADAMS R. D and SOLOMON H. C. *Neurosyphilis*, Oxford University Press, New York, 1946

MOORE, J E., and WOODS A. C. "Pathology and Pathogenesis of Syphil tic Primary Optic Atrophy Critical Review" *Am. J Syph. Gonor & Ven Dis.* 24 59 1940

NEEL, A. V *The Content f Cells and Proteins n the Normal Cereb ospinal Fluid The Diagnostic Importanc f Demonstrat ng Small Pathological Changes in the Cells and Proteins The Technique of the Investigation* Munksgaard Copenhagen, 1939

NICOL, W D. Penicillin in General Paresis," *Brit M J* 1 734 (May 24) 1947

O'LEARY P A. Penicillin in the Treatment of Syphilis *M Clin. North America*, 30 895 1946.

——— BRUNSTING L. A. and OCKERLY O "Penicillin in the Treatment of Neurosyphilis, *J.A.M.A.* 130 698 1946.

PARKHURST G E., and BOWMAN R W "Treatment of Neurosyphilis at Hot Springs Medical Center Arkansas, *J Ven. Dis. I form.* 29 159 1948.

REINER, E. R., and WEICKHARDT G D "Penicillin Therapy in Neurology and Psychiatry *M A District f Col mbia*, 15 488, 1946

REYNOLDS, F W Penicillin in the Treatment of Syphilis," *Am. J M d.*, 1 661 1946.

——— MOHR, C. F and MOORE, J E Penicillin in the Treatment of Neurosyphilis, *J.A.M.A* 131 1255 1946.

ROSE, A. S Penicillin Treatment of Neurosyphilis," *C ecticut M J* 9 522, 1945

——— and SOLOMON H. C Penicillin i the Treatment of Neurosyphilis," *J.A.M.A* 133 5 1947

——— and ——— Neurosyphilis, *Am J Psychiat.*, 103 524 1947

——— TRU TT L. D HINDLE, J A PROUT C. and SOLOMON H. C. "Penicillin Treatment of Neurosyphilis, *Am. J Syph G r & Ven. Dis.* 29 487 1945.

SCULLY J P FALK, M S and STOKES J H "The Serologic Response in Penicillin-treated Symptomatic Neurosyphilis," *Am. J Syph. Gonor & Ven. Dis* 32 224 1948

SOLOMON H. C. "Penicillin in Neurology & Psychiatry" *Dig Neurol & Psychiat* Hartford Institute of Living 14 132, 1946

STERN J E., and CAMPBELL, H M. Early Effects of Penicillin Treatment of Dementia Paralytica," *Arch Neurol. & Psychiat* 55 266, 1946.

TAPELLA, P A. URIA J S. and TAMBORINI, R. L. La penicilina en el tratamiento de la neurosifilis," *Prensa med argent* 34 240 1947

TUCKER, H. A. and ROBINSON R. C. "Neurosyphilitic Patients Treated with Penicillin Probable Herxheimer Reactions," *J.A.M.A.* 132 281 1946.

CHAPTER 14

SYPHILIS AND PREGNANCY

THE prevention of congenital syphilis is one of the major goals of syphilis control. Laws requiring blood tests for syphilis in pregnant women are now more than ever justified, because the advent of penicillin has made it possible to prevent the birth of a syphilitic child in almost 100 per cent of cases with proper prenatal care. The increased sensitivity of STS may rarely lead to incorrect diagnosis of syphilis in a pregnant woman, but it is far better that an occasional error of this sort occur than that syphilis go undetected during pregnancy The routine testing of all pregnant women is a small price to pay for the prevention of the tragedies of congenital syphilis.

OUTCOME OF PREGNANCY IN THE SYPHILITIC WOMAN

Pregnancy in a syphilitic woman may have one of the following outcomes (1) a late abortion at any time after the fourth month of pregnancy (2) a stillborn child at term (3) a living syphilitic baby born prematurely or at term or (4) an uninfected living child.

Late abortion and stillbirth.—The available evidence indicates that the fetus is infected with syphilis only after the sixteenth week of pregnancy A syphilitic fetus under 4 months of age has rarely been reported. For this reason, other causes than syphilis should be sought in women who miscarry during the early months of pregnancy Late abortion due to syphilis is usually accompanied by pathologic changes in the placenta. Although grossly normal placentas have been noted in deliveries of syphilitic babies it is probable that some area of the placenta is always infected in such cases. The syphilitic placenta usually has a characteristic appearance t is pale, edematous, and disproportionately enlarged. The chorionic villi are enlarged and filled with round and oval connective-tissue cells the blood vessels show a h gh degree of endarteritis which, in turn, impairs the blood supply to the fetus. Premature deliveries of a macerated fetus, swarming with T pallida, ha e frequently occurred in

Scully J P Falk, M S. and Stokes J H "The Serologic Response in Penicillin-treated Symptomatic Neurosyphilis," *Am J Syph Gonor & Ven. Dis* 32 224 1948.
Solomon H. C. Penicillin in Neurology & Psychiatry" *Dig Neurol & Psychiat.*, Hartford Institute of Living 14 132 1946
Stern J E., and Campbell, H M Early Effects of Penicill n Treatment of Dementia Paralytica," *Arch Neurol. & Psychiat.*, 55 266, 1946.
Tapella, P A. Uhia, J S and Tamborini, R. L. "La penicillina en l tratamiento de la neurosifilis," *Prensa med argent.*, 34 240 1947
Tucker, H. A., and Robinson R C. "Neurosyphilitic Patients Treated with Penicillin Probable Herxheimer Reactions, *J.A.M.A* 132 281 1946.

series. Furthermore, I have had no reason to believe that neurosyphilis is less frequent in women who have been pregnant than in those who have had no pregnancy. Doctor Mortimer D. Speiser, who has had charge of the prenatal syphilis clinic at Bellevue Hospital for many years, has long been skeptical that pregnancy has a beneficial effect on syphilis. It is true that Brown and Pearce observed that pregnancy altered the course of syphilis in rabbits. They found that early lesions were less frequent and less prominent following inoculation of pregnant rabbits than of nonpregnant rabbits. The effect of pregnancy on syphilis, however, is of minor importance, and more of academic than of practical interest. The important point is that syphilis can have disastrous effects in pregnancy, even in the absence of clinical manifestations.

DIAGNOSIS

Syphilis in the pregnant woman is diagnosed in the same way as is syphilis in other individuals, i.e., by history, physical examination, and laboratory tests. Early syphilis can be diagnosed by dark field examination of accessible lesions. In latent syphilis, of course, the diagnosis is made only by means of positive STS and history. The importance of positive STS in pregnancy cannot be overemphasized. Stillborn syphilitic fetuses and syphilitic children have been delivered of mothers who appeared to be in perfect health and denied a history of syphilis, but who had positive STS. It would be foolhardy to disregard positive STS in a pregnant woman, despite absence of suggestive history and clinical manifestations.

Reliability of STS during pregnancy.—The claim has been made that pregnancy causes biologic false positive STS in rare cases. The evidence for this statement is at present unconvincing. Certainly biologic false positive tests have occurred in women during pregnancy just as they have in other individuals. There is no proof, however, that pregnancy itself was the cause of such false positive tests. Within recent years I have observed two women who probably had biologic false positive STS during pregnancy. In both cases extramarital sexual relations were denied, and the spouse had negative STS. Each was treated for syphilis with penicillin without any effect on the strongly positive STS, and each was delivered of a normal baby. Two and three years, respectively, after delivery both women had quantitative STS as high as when first discovered. One had received large amounts of bismuth and arsenicals in addition to 10,000,000 units of penicillin. I am convinced that both

women have biologic false positive serologic reactions for syphilis, and that pregnancy was not responsible for the reagin in their blood.

In spite of the undisputed occurrence of biologic false positive tests, every instance of positive STS during pregnancy must be regarded as of possible serious import. Now that penicillin is available, it is perhaps wiser to treat some cases of very questionable syphilis during pregnancy than to miss treating a true case. As will be shown later in this chapter it is not essential to treat all pregnant women who have had previous adequate antisyphilitic treatment, but the safest rule to follow is to treat with penicillin if there is any question of a possibly active infection during pregnancy

Seronegative syphilis in the pregnant woman.—In former years when blood tests for syphilis were considerably less sensitive than now reports of syphilitic babies born of seronegative women were not infrequent. Consequently it was generally believed that every woman with a history of syphilis, regardless of past treatment and serologic status, should be given antisyphilitic treatment during pregnancy Although this belief is outmoded, it is still not safe to ignore a history of syphilis in a seronegative pregnant woman. If the patient has had previous positive STS and previous antisyphilitic treatment, decision as to the necessity for additional treatment during pregnancy depends on when the previous treatment was administered and on the amount and kind of treatment. If the patient received good treatment for early syphilis within the previous year and the STS became and remained negative, re treatment is unnecessary during pregnancy unless relapse occurs. To detect relapse, STS must be made at no less than monthly intervals throughout pregnancy If the patient was originally treated for late syphilis and subsequently became seronegative, it is unlikely that further treatment will be needed during pregnancy If treatment is withheld in seronegative cases with a history of treated syphilis, repeated STS should be taken throughout pregnancy Certainly a woman who has become seronegative and has had previous normal pregnancies and normal children need not receive *antisyphilitic treatment during subsequent pregnancies. However* if there is any doubt in the mind of the physician as to the activity of the case, it is wiser to give penicillin than to face the risk of a congenital syphilitic infant being born.

Paternal transmission of syphilis.—The spermatozoa of a syphilitic father cannot transmit syphilis directly to the fetus. Syphilis of the fetus is always derived from an infection of the mother The question occasionally arises whether or not to treat the pregnant wife of a syphilitic

husband, when the wife is seronegative and has no history or signs of syphilis. Treatment in such cases is unnecessary provided that monthly STS remain negative throughout pregnancy If the husband was recently infected and had had sexual relations with his wife during her pregnancy it would be safe as a rule to withhold treatment from the wife until a definite diagnosis could be made. However now that penicillin is available, I advise treating such a case without waiting for signs of the infection to appear the possibility of infection is sufficiently great to warrant the relatively easy and safe treatment with penicillin. This is especially true of women who may have become infected in the last trimester of pregnancy

PENICILLIN THERAPY OF SYPHILIS IN PREGNANCY

The ideal plan of antisyphilitic therapy in the pregnant woman, as outlined by Speiser should include the following

1 *Freedom from serious toxic effects*
2. Prevention of the transmission of the disease from mother to baby
3 Cure of the maternal syphilis
4 Cure of the congenital syphilitic child in utero in cases beyond the sixteenth week of pregnancy when syphilis may have already been transmitted to the fetus
5 Adequate therapy in a short time

That penicillin best fulfills these requirements has been proved by the reports of the treatment of syphilitic women during pregnancy from numerous centers, notably Johns Hopkins Hospital, the University of Pennsylvania Hospital, and Bellevue Hospital.

The table in Fig 66 shows the results obtained in 172 pregnant women treated in Bellevue Hospital during the early years of penicillin therapy when smaller total doses of penicillin were used than are now advised. This table was published by Speiser and his coworkers in the June, 1947 issue of *The Journal of Venereal Disease Information.* We now have the results of pregnancies of 305 women treated for syphilis during pregnancy but a complete analysis of these cases has not yet been made. I can report, however that 8 babies were born with congenital syphilis, an incidence of 2.6 per cent. The incidence of late abortions, stillbirths and neonatal deaths in the series was less than 10 per cent, but complete information regarding the cause of the various disastrous results was still under investigation at the time this chapter was written. From the

FIG. 66. RESULTS OF TREATMENT OF

TREATMENT SCHEDULE	DIAGNOSIS	NUMBER OF PATIENTS	DURATION OF PREGNANCY AT ONSET OF TREATMENT			TERM
			LESS THAN 16 WEEKS	16 TO 32 WEEKS	MORE THAN 32 WEEKS	
600,000 units penicillin (10 000 u. q 3 hours for 60 doses)	Primary and/or secondary	9	1	8		8
	Latent	0				
1,200 000 units penicillin (40,000 u. q 6 hours for 30 doses)	Primary and/or secondary	30	11	17	2	26
	Latent	3	1	2		1
1,200 000 units penicillin (20,000 u q 3 hours for 60 doses)	Primary and/or secondary	12	1	8	3	12
	Latent	4	1	2	1	4
1,200,000 units penicillin (20 000 u. q 3 hours for 60 doses) and arsenoxide (0 04 × 8)	Primary and or secondary	43	10	29	4	38
	Latent.	3	1	2		3
2,400,000 units penicillin (40,000 u q 3 hours for 60 doses)	Primary and or secondary	6	1	5		4
	Latent	2		1	1	2
4 000 000 units penicillin (40 000 u q 3 hours for 100 doses)	Primary and/or secondary	23	2	16	5	20
	Latent	14	1	10	3	13
Totals	Primary and/or secondary	123	26	83	14	108
	Latent	26	4	17	5	23
	All diagnoses	149	30	100	19	131
	Percentages	100 0	20 0	67 0	3 0	88.0

Follow-up of less than 16 weeks, but no evidence of syphilis from physical
An additional 23 patients were treated more than once during pregnancy because
of the 23 pregnancies resulted in syphilitic babies, 2 ended in late abortion and 1
in the fetuses.

RESULT OF PREGNANCY					
PREMATURE	NON SYPHILITIC BABY	"PROBABLY NON SYPHILITIC"	DISASTROUS RESULT NOT OWING TO SYPHILIS	CONGENITAL SYPHILIS	DISASTROUS RESULT "POSSIBLY OWING TO SYPHILIS
1	8				1 neonatal death at 10 weeks—cause unknown
4	26		1 neonatal death t 14 weeks 1 early abortion		2 late abortions—no information 1 late abortion—no information
2			1 early abortion	1	
	10			2	
	4				
5	37	1 (then acquired syphilis)	2 neonatal deaths at 2 and 11 weeks 1 late abortion 2 stillbirths at 34 weeks and term		
	3				
2	4	1 (neonatal death of burns)			
	2				
3	10	10	1 stillbirth at 34 weeks		1 late abortion—no information
1	10	4			1 neonatal death (premature)—no information
15	95	12	9	2	5
3	19	4	1	1	1
18	114	16	10	3	6
12 0	76.5	10.7	6.8	2 0	4 0

examination, serologic tests, or X rays of long bones.
of relapse or reinfection. One woman relapsed twice and was re treated twice. None
in a stillbirth, but no information was obtained regarding the presence of syphilis

began to multiply at a normal rate after the mother delivered. The occurrence of relapses subsequent to delivery is another reason for giving additional penicillin therapy late in the course of pregnancy We have not adopted this policy on our service, and I have no data regarding the amount of additional treatment that should be given after the original course of penicillin, but I believe that, following an original treatment of 4 000 000 units of penicillin, one or two injections of 600 000 units of procaine penicillin G in oil and 2 per cent aluminum monostearate during the last 4 weeks of pregnancy would protect both mother and child, with rare exceptions.

Cure of the congenital syphilitic child in utero.—There is no doubt that penicillin therapy of the mother during pregnancy is effective in syphilis which has already been contracted by the fetus in utero Numerous investigators have demonstrated that penicillin is transmitted through the placenta. The majority of pregnant women managed by us were treated in the latter half of pregnancy Again referring to Fig 66 it will be seen that 97 women were treated for dark field positive early syphilis after the fourth month of pregnancy and 14 of these were treated during the last 4 weeks of pregnancy In addition, 23 patients were re-treated for relapse or reinfection late in pregnancy It is inconceivable that the fetus escaped infection in a high percentage of these cases of maternal early syphilis. Yet only 2 babies had congenital syphilis at birth, and they were born of mothers who relapsed after treatment and showed no evidence of the relapse until after delivery Cases have been observed in which X rays revealed healing bone lesions and the STS were positive, and without additional postnatal therapy these infants never developed signs of syphilis and the STS became negative. Thus, there is good reason to believe that penicillin has cured infections of the fetus in utero.

Adequate therapy in a short period.—Obviously penicillin fulfills the requirement of adequate therapy in a short period better than any previously known antisyphilitic treatment. Speiser Wexler Asher and I *reported the results of massive arsenotherapy of early syphilis during* pregnancy in a small series of 30 women treated in a 10-day period. Good results were obtained in a minimum of 76.6 per cent, and possibly 85 per cent, if a late abortion was not considered as caused by syphilis. In all, we treated 43 pregnant women with massive arsenotherapy in a period of 10 days and had 1 death from arsenical encephalopathy after which this type of therapy was abandoned during pregnancy

Thus, the advent of penicillin has been a great boon in the treatment

of syphilis complicated by pregnancy In former years reactions to arsenical drugs, especially gastrointestinal reactions, were very frequent in pregnant women and many syphilitic women received inadequate treatment because of such reactions. As previously noted, penicillin has given satisfactory results in at least 94 per cent of 305 women treated for either early or late syphilis and, if additional therapy had been given during the late months of pregnancy even better results would undoubtedly have been obtained.

MANAGEMENT OF PREGNANT WOMEN WHO RECEIVED ANTISYPHILITIC TREATMENT PRIOR TO PREGNANCY

In the great majority of cases, pregnant women who have received previous antisyphilitic treatment, considered to be adequate by the usual standard of therapy do not require additional treatment during pregnancy This fact has been well proved on our service, but, when in doubt about the status of a case, it is better to give penicillin during pregnancy than to run even a small risk of congenital syphilis. Among the women treated for early syphilis with penicillin, on our service, the results of the pregnancies of 221 women who became pregnant subsequent to therapy and were permitted to go untreated during pregnancy are now known. Only 1 baby was born with congenital syphilis in this series. The single failure occurred in a woman who had been treated for early syphilis 2 months before she became pregnant. Her quantitative Kahn test at the seventh month of pregnancy was 32 but she showed no evidence of relapse. She was not seen again until she delivered, at which time her quantitative Kahn test was 128 and she had dark field positive lesions. The occurrence of even 1 congenital child in 221 cases is sufficient reason for being cautious about advising against treatment during pregnancy in previously treated patients who still have positive STS. If such patients are observed regularly throughout pregnancy with quantitative STS relapses will be detected in most cases, and treatment can be given. In patients treated for early syphilis, within a few months before becoming pregnant, continuous observation throughout pregnancy is especially important. In spite of the excellent results obtained by us in previously treated women who had no antisyphilitic therapy during subsequent pregnancy I am not ready to advise against further treatment of such cases, especially since treatment with penicillin is so easy and safe. Syphilologists of great experience are undoubtedly justified in not treat

ing previously treated seropositive women during pregnancy but the safest general rule to follow in pregnant seropositive cases is to give penicillin when there is any doubt as to activity of the infection.

TREATMENT SCHEDULES

Both early and late syphilis in pregnancy should be treated with a minimum of 4 000 000 units of penicillin over a period of not less than 12 days when aqueous solutions or POB are used. With procaine penicillin G in oil and 2 per cent aluminum monostearate, the period of therapy can be extended, if desired, by giving two or three injections of 600,000 units a week for 3 to 4 weeks.

REFERENCES

BROWN W H., and PEARCE, L. "Reaction of Pregnant and Lactating Females to Inoculation with Treponema Pallidum A Preliminary Note," *Am. J Syph* 4 593 1920

COLE, H. N; AYRES S. III BARR, J H. GENATIOS R. HELD, B. MURPHY W W PRINTZ, D R. and STRAUCH J "Use of Penicillin in the Treatment of Syphilis in Pregnancy" *Arch. Dermat & Syph.*, 54 255 1946.

CROSS R. G "Repeated Abortions, Miscarriages and Stillbirths Value of Antisyphilitic Treatment," *Lancet* 2 754 1946.

GOODWIN M S and MOORE, J E. "Penicillin in Prevention of Prenatal Syphilis, *J.A.M.A.*, 130 688 1946.

GREEN H J and HOBBY G L. "Transmission of Penicillin through Human Placenta" *Proc Soc Exper Biol. & M d* 57 282 1944

HUTTER, A. M and PARKS J "The Transmission of Penicillin through the Placenta A Preliminary Report," *Am. J Obst & Gynec* 49 663 1945.

INGRAHAM N R., JR. STOKES J H. BEERMAN H. LENTZ, J W and WAMMOCK, V S Penicillin Treatment of the Syphilitic Pregnant Woman," *J.A.M.A* 130 683 1946.

INGRAM C. H. "Syphilis in Pregnancy Treated by Penicillin," *Am. J Obst & Gyn c* 53 881 1947

LEAVITT H M. "Clinical Action of Penicillin on the Uterus," *J Ven. Dis. Inform.*, 26 150 1945.

LENTZ, J W INGRAHAM N R., JR. BEERMAN H. and STOKES J H. "Penicillin in the Prevention and Treatment of Congenital Syphilis Report on Experience with the Treatment of Fourteen Pregnant Women with Early Syph lis and Nine Infants with Congenital Syphilis," *J.A.M.A* 126 408 1944

MOORE, J E. *Modern T eatment f Syphilis* 2nd ed., Charles C. Thomas, Publisher Springfield Ill., 1943

OLANSKY S., and BECK R. "Rapid Treatment of Prenatal Syphilis," *Am. J Syph., Gonor & Ven Dis* 31 51 1947

SPEISER, M. D FLAUM G MOON ADAMS D and THOMAS E. W Penicillin Therapy for Syphilis in Pregnancy" *J Ven. Dis. Inform.*, 28 108 1947

——— and THOMAS, E. W "Regarding the Unusual Effect of Penicillin Therapy upon the Uterus," *J Ven. Dis. Inform.*, 27 20 1946.

——— WEXLER, G THOMAS E. W; and ASHER, H. A. "The Rapid Treatment of Early Syphilis during Pregnancy" *Am. J Obst & Gynec.*, 49 214 1945

WOLTZ, J H. E., and WILEY M. M. "The Transmission of Penicillin to the Previable Fetus Its Significance in Prenatal Syphilis," *J.A.M.A* 131 969 1946

——— and ZINTEL, H. A. "Transmission of Penicillin to Amniotic Fluid and Fetal Blood in the Human," *Am. J Obst & Gynec.*, 50 338 1945

3 Bilateral symmetrical osteomyelitis of the proximal medial aspects of the tibiae
4 Multiple 'separation of epiphyses with or without impaction in bones which are not rachitic" *

In spite of the diagnostic characteristics of osseous lesions in many cases of congenital syphilis, it is never wise to rely solely on roentgenograms of the bones for the diagnosis. In all cases every possible factor must be taken into consideration in making a diagnosis. When associated with positive STS of the baby's blood bone and cartilage lesions are usually due to syphilis, unless some other cause of the bone changes can be proved.

The most frequent syphilitic lesion in the newborn child is osteochondritis. In such cases the roentgenogram shows varying degrees of destruction and increased density of bone, the sawtooth metaphysis being one of the most characteristic features. Osteochondritis is always associated with periostitis, which may or may not be apparent in the roentgenogram as an elevated shadow on the surface of the bone. Neither osteochondritis nor periostitis in the newborn baby results in serious sequelae. By the eighth month of life, X ray examination of the bones shows no trace of a previous osteochondritis or periostitis. On the other hand early lesions of the skull, the bones of the face, and the shafts of the long bones may persist for months and may cause a marked overproduction of bone. Osteitis of the tibias, frontal bones, maxillas, and mandibles may produce overgrowth of bone which persists for life. Rarely a severe type of osteitis of the phalanges (syphilitic dactylitis) develops during the first 2 years of life. In many cases, however the early osseous lesions of congenital syphilis heal without demonstrable sequelae.

Liver and spleen.—Enlargement of the liver and spleen is found very frequently in congenital syphilis of the newborn child. The hepatosplenomegalia is not diagnostic of congenital syphilis, as other conditions may cause it. Icterus is rarely associated with the hepatitis of congenital syphilis, but edema may develop because of a lowered serum protein. Hepatic insufficiency in severe cases may be one of the factors causing neonatal deaths.

Meninges.—Meningitis, with or without clinical signs, has occurred in from 40 to 50 per cent of babies born with congenital syphilis. The diagnosis is made by spinal fluid examination. Early congenital syphilitic

* Moore, J E *Modern Treatment of Syphilis* 2nd ed., Charles C. Thomas, Publisher Springfield Ill 1943 p 484

involvement of the central nervous system may be asymptomatic, or may cause convulsions, stiffness of the neck, positive Kernig's signs, and hydrocephalus.

Eyes.—Rarely iritis has been reported in infants with congenital syphilis, and choroiditis is also said to have occurred during the early period of infection. As a rule, however chorioretinitis is a late rather than an early manifestation of congenital syphilis.

DIAGNOSIS OF CONGENITAL SYPHILIS IN THE NEWBORN

When skin or mucous-membrane lesions are present, the diagnosis of congenital syphilis can easily be made by dark field examination. If a dark-field microscope is not available, the presence of cutaneous or mucous-membrane lesions associated with positive STS of the baby's blood suffice to establish the diagnosis.

In the absence of clinical signs of syphilis, a diagnosis of congenital syphilis cannot be made in the newborn child solely on the basis of positive blood tests for syphilis.

Reagin from the mother's blood is frequently transmitted to the child while in utero, with the result that positive STS may be found in an uninfected baby at birth. A healthy baby should not be diagnosed as syphilitic unless the STS are positive 3 months after birth or the quantitative STS show an increasing amount of reagin. In babies with reagin passively transmitted from the mother the quantitative STS show a progressive fall in titers.

The transmission of reagin from the mother's blood to the baby is one of the numerous perplexing problems in syphilis. In some cases the mother may have large amounts of reagin in her blood without transmitting it to the baby while in others reagin is unquestionably transmitted to the baby from the maternal blood. Our records reveal that a mother with quantitative Kahn tests of 64 or more, may give birth to a nonsyphilitic baby who has very small amounts of reagin in its blood at birth another mother with relatively low quantitative Kahn tests may have a nonsyphilitic baby with higher Kahn titers than the baby born of the mother with a large amount of reagin The reason for these discrepancies is obscure. It is, of course, probable that in some cases the baby may have acquired syphilis in utero and have been cured by the treatment of the mother during her pregnancy But we have found that reagin was transmitted from mother to fetus in cases where no antisyphilitic treatment was given during pregnancy In these cases the baby became

seronegative spontaneously within 3 months after birth. Possibly the transmission of reagin from the mother to fetus depends to some extent on the permeability of placental vessels, which varies in different individuals during pregnancy Other factors may well influence the transmission of substances from the maternal blood to the fetus. A study of this problem is now being made at Bellevue Hospital by Speiser and Rein

In past years congenital syphilis has been missed because of the failure to take blood for STS from the baby but it is also true that healthy nonsyphilitic babies have been misdiagnosed as syphilitic because of the failure to recognize that positive STS in the baby were due to the passive transfer of reagin from the mother Before making the diagnosis of congenital syphilis in the newborn child, in the absence of syphilitic lesions, it is imperative that every factor be taken into consideration especially the maternal history Where the only positive finding in the infant is positive STS, there is no harm in delaying treatment for a 3-month period to determine whether or not the reagin is due to passive transfer from the mother Cures of asymptomatic syphilis of babies can be obtained by starting treatment during the fourth month of life in as high a percentage of cases as when treatment is started during the first weeks, although it may take a longer time for the blood to become seronegative when treatment is delayed for 3 months.

Cord blood STS.—Unless taken with great care, cord blood is less satisfactory for STS than blood withdrawn from the baby during the first week after birth. Frequently samples of cord blood are hemolyzed, and the blood is contaminated with tissue cells and fluid from the cord. Sometimes the maternal blood which has flowed over the cord becomes mixed with the cord blood. When cord blood is carefully taken and tested, however the STS should give the same results as on blood withdrawn from the baby's vein at birth.

LATE MANIFESTATIONS OF CONGENITAL SYPHILIS

The course of congenital syphilis after infancy is in most respects similar to that of syphilis acquired after birth. There are, however certain unique features about the late manifestations of congenital syphilis that are due to developmental changes which take place during infancy The first unique characteristic of congenital syphilis is the immunity of the cardiovascular system to syphilitic inflammation. I have never seen cardiovascular syphilis in a congenital syphilitic. Cases have been reported in the literature, but well-documented evidence of cardiovascular syphilis in proved congenital syphilitics is extraordinarily rare. Thus, the

developing aorta in the infant resists the syphilitic infection and acquires a permanent immunity to future syphilitic inflammation.

Interstitial keratitis.—Unfortunately the unique features of congenital syphilis do not end with the protection of the cardiovascular system. For unknown reasons, a syphilitic infection during infancy makes some individuals peculiarly susceptible to a later involvement of the cornea. As noted in the section on interstitial keratitis in Chap. 11 the pathogenesis of this phenomenon is unknown. Probably the syphilitic infection during infancy causes some obscure developmental change in the cornea which makes it liable to vascularization from a variety of causes later in life. On our service, interstitial keratitis has been observed in congenital syphilitics from 9 to 31 years of age. Pediatricians have reported it in children at any time after infancy The course and treatment of the disease were described in Chap. 11

Bilateral hydrarthrosis (Clutton's joints)—A bilateral hydrops of the joints, especially of the knees, was described by Clutton in 1886 as one of the unique manifestations of congenital syphilis. The condition is caused by a syphilitic synovitis and is not associated with bone or cartilage involvement. It is painless, but the joints are swollen because of the fluid. The hydrops responds readily to antisyphilitic treatment. A destructive type of polyarthritis in late congenital syphilis was described by both von Gies and Fournier but cases of this kind have rarely been reported in this country

Late congenital neurosyphilis.—Late congenital syphilis of the central nervous system is similar to that of acquired syphilis and presents no unique features. The diagnosis depends on spinal-fluid examinations. Syphilitic involvement of the central nervous system may be present for years before signs and symptoms develop. Any of the clinical syndromes described in Chap. 13 may develop. Meningitis or meningovascular syphilis may cause eighth-nerve deafness in children. Eighth-nerve deafness in congenital syphilitic children was observed fairly frequently during the last century today it is relatively rare. The signs and symptoms of general paresis in congenital syphilitics may occur at any time after the fifth year of life, but juvenile general paresis is rarely diagnosed until the teens, and I have seen several cases of general paresis in congenital syphilitics during their late twenties.

Gummas and gummatous infiltrations.—Congenital syphilis provides no protection against the development of gummas and gummatous inflammations at any time after the first 2 years of life. The inflammatory reactions are similar to those described in late acquired syphilis. The

incidence of such lesions in late congenital syphilis is similar to that of acquired syphilis.

STIGMATA OF CONGENITAL SYPHILIS

The stigmata of congenital syphilis observed in children and adults are due to scars of early lesions and to developmental changes caused by the early infection.

Frontal bosses.—Syphilitic involvement of the frontal bones of the skull during infancy may cause a compensatory overgrowth of bone reflected in a bulging of the forehead, or more frequently in a bulging of the upper half of the frontal bones. This condition is known as frontal bosses, and it is one of the most frequent of congenital syphilitic stigmata. Frontal bosses, however are not diagnostic of congenital syphilis. At most they are suggestive their presence may give support to the diagnosis of congenital syphilis when associated with other evidences of the disease

Facies.—Early syphilitic involvement of the bones of the head may produce changes causing fairly characteristic facies. Destructive processes in the nasal bones may cause a breakdown of the bridge of the nose or may prevent the bridge from developing normally The resultant deformity is known as saddle nose. The saddle nose of congenital syphilis is usually associated with an overgrowth of the frontal bones, maxillas, and mandibles, giving a characteristic facial appearance.

Rhagades.—As previously noted, the early cutaneous lesions of congenital syphilis may be destructive. Eczematous, fissured lesions about the mouth, oftentimes extending to the cheeks and chin, heal with linear scars known as *rhagades*. Similar scars are occasionally seen about the anus. *Rhagades are infrequently seen now but they constitute a characteristic stigma of congenital syphilis when present.*

Dental dystrophies.—The development of the permanent teeth may be impaired by a syphilitic infection during the early weeks of life. The first teeth escape the effects of the infection, but the tooth buds of the permanent teeth may be injured. The buds of the incisors and sixth-year molars are in an active stage of development at birth or during the first weeks of life. As a result, they are the most likely to be involved by the syphilitic infection. But most of the permanent teeth may suffer in some cases. The enamel of the teeth is poor and the teeth may be badly formed oftentimes they are spaced far apart. The teeth decay easily and may have to be pulled during the second or third decade of life. Poorly formed, widely spaced, and easily decayed teeth are suggestive

but not diagnostic of congenital syphilis. The characteristic congenital syphilitic stigma occurs in the incisors, which are rounded and peg shaped, and have a notch in the middle of the biting surface (Hutchinson's teeth)

Saber shin.—Early congenital syphilitic osteitis may cause a bowing of the shafts of the tibias which is followed by an overgrowth of bone, giving a bulky saber-shaped shin Saber shins are not diagnostic of congenital syphilis, but they are one of the definite stigmata of the disease. Enlargement or thickening of the inner thirds of the clavicles caused by overgrowth of bone following a congenital syphilitic osteitis of the clavicles is also listed among the stigmata of congenital syphilis.

THIRD-GENERATION SYPHILIS

By adult life, congenital syphilis is rarely infectious, even sexually Women with congenital syphilis usually do not transmit the infection to the fetus during pregnancy but they may do so occasionally We have several well-documented cases of third-generation congenital syphilis in our records at Bellevue Hospital.

DIAGNOSIS OF LATE CONGENITAL SYPHILIS

The stigmata of congenital syphilis aid in making the diagnosis, but oftentimes no stigma is present in patients who were infected in utero. I have observed numerous cases of severe symptomatic neurosyphilis in congenital syphilitics who had no stigmata of the disease. The most important factor in the diagnosis of late congenital syphilis is a good history including a complete family history Reports of the STS of every member of the family should be obtained when congenital syphilis is suspected. The investigation of the family in such cases has frequently had fruitful results in case finding.

In some cases of late latent syphilis, a possible congenital origin of the infection can neither be ruled out nor proved. From the point of view of the medical aspects of the disease, late latent congenital syphilis is no more to be feared than late latent acquired syphilis, and it requires no more treatment than the latter The STS titers of congenital syphilitics over 12 years of age, seen on our service, have varied from 0 to over 2,000 There has been no relationship between the height of the titer and the severity of the disease. I have no accurate information as to the frequency with which congenital syphilitics become seronegative spontaneously Symptomatic congenital syphilis of patients with negative STS

is very rare I have observed it only in cases of tabes dorsalis. As a rule, seropositive adults with congenital syphilis will remain seropositive for many years after treatment, if not for their lifetime.

TREATMENT OF INFANTILE CONGENITAL SYPHILIS

Excellent results have been obtained with penicillin in the treatment of congenital syphilitic infants. The reports of a co-operative study headed by Platou, comprising five clinics (Tulane, Johns Hopkins, University of Pennsylvania, Emory University and the University of Texas) show that, even in relatively small doses, penicillin has been very effective in the treatment of 252 infants with congenital syphilis. The total doses of penicillin used in the treatment of these cases varied from 20 000 to 150 000 units per kilogram. Sodium penicillin in aqueous solution was used, and individual injections were given every 3 hours for periods varying from 7½ to 15 days. The report of the co-operative group in January 1947 stated that 73 per cent of 252 patients had had satisfactory results following a single course of penicillin, 17.9 per cent were still undetermined, and only 9 1 per cent were considered unsatisfactory The unsatisfactory results included 5 deaths which occurred within 14 days after penicillin treatment was started. Clinical and serologic relapses occurred in only 6 cases (2 4 per cent) The relapses were noted as early as 3 months and as late as 11 months after treatment. The authors concluded that young syphilitic infants should receive a total dosage of at least 100 000 units of penicillin per kilogram, over a period of 12 to 15 days, and that individual injections of aqueous solutions should be given every 3 hours.

The occurrence of less than 3 per cent relapses following penicillin therapy of infantile congenital syphilis is much less than that following penicillin treatment of early syphilis in adults. It is impossible to prove that the marked difference is due solely to reinfection among the adults, but I am increasingly of the opinion that reinfections explain the higher relapse incidence in adults. Possibly the growing infant develops a greater resistance to the T pallidum than the adult, but the evidence for this hypothesis is not very convincing The incidence of neonatal deaths among syphilitic infants was much higher when antisyphilitic treatment consisted of bismuth and arsenicals, partly because of the difficulty of treatment. Babies with clinical manifestations of congenital syphilis should receive penicillin at once. Delay in such cases may be fatal.

Treatment schedules.—If aqueous solutions of penicillin are used, a minimum total dose of 100,000 units per kilogram should be given over

a period of at least 12 days with individual injections every 3 hours. From present indications, procaine penicillin G in oil and aluminum monostearate provides an even more ideal therapy for early congenital syphilis than do aqueous solutions. It is possible that injections of 150 000 to 300 000 units of procaine penicillin G in oil and aluminum monostearate at intervals of 4 or 5 days for three injections will give as good results as injections of aqueous solutions every 3 hours for 15 days. The Pediatrics Service at Bellevue Hospital recently adopted such a schedule for study purposes. Should the results be satisfactory the treatment of congenital syphilis becomes relatively easy

TREATMENT OF LATE CONGENITAL SYPHILIS

The treatment of late congenital syphilis is the same as that of late acquired syphilis. In children, the dosage of penicillin should be adjusted to weight.

REFERENCES

Hill, A. J., Jr. Platou R. V and Kometani J T "Osseous Syphilis Effect of Penicillin on Rate of Healing," *J Pediat* 30 547 1947

Moore-Adams D "False Serologic Tests for Syphilis in Infants of Treated Mothers, *New York State J Med* 48 1819 1948.

Platou R. V Hill, A. J Ingraham N R. Jr. Goodwin M. S. Wilkinson E. E. Hansen A. E. and Heyman A.: "Early Congenital Syphilis Treatment of 252 Patients with Penicillin, *J.A.M.A* 133 10 1947

Yampolsky J "Newer Concepts in Management of Congenital Syphilis in Children," *M Clin. North America*, 31 636 1947

——— and Heyman A. "Penicillin in the Treatment of Syphilis in Children, *J.A.M.A.*, 132 368, 1946.

CHAPTER 16

THE PUBLIC HEALTH ASPECTS OF SYPHILIS

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CHAPTER 16

THE PUBLIC HEALTH ASPECTS OF SYPHILIS

SYPHILIS measured by any standard is a major public health problem. It leads many diseases and is outranked by few in terms of prevalence, disabling or fatal consequences (if untreated) and economic cost.

The human cost of this controllable disease is suggested by the thousands of deaths reported annually from syphilis, the thousands of persons who are paralyzed or confined to mental institutions, and the thousands of children born with congenital syphilis. Syphilis in 1945 caused more deaths than the combined totals for poliomyelitis, rheumatic fever malaria, diphtheria, cerebrospinal meningitis, typhoid and paratyphoid, whooping cough, scarlet fever pellagra, alcoholism and dysentery The reported death total for syphilis was more than 14 000

The material loss is hinted at in estimates that it costs $11 000 000 a year to support syphilitics in mental hospitals * and $4 000,000 a year to support the syphilitic blind.† Bigger material costs are suggested by Iskrant's estimate that the loss of income from paresis alone is more than $112 000 000 annually and Rice s estimate that the annual loss of income from syphilitic blindness is $6 000 000

Yet many people with syphilis do not seek diagnosis and treatment when they first get the disease, because of ignorance, indifference, fear or lack of money They continue to spread the germ at this early stage when it is most infectious and when treatment is most effective. Any program for controlling syphilis must bring these people to physicians who can diagnose and treat them It must include clinics, laboratories, drugs, equipment, and trained personnel for those patients who cannot obtain private medical attention. It must encourage others to go to their

* ISKRANT ALBERT P "The Economic Cost of Paresis in the U.S (calculated for 1940) *J Ven. Dis. I form* 26 175–183 1945

† RICE, C. E. "Cost and Loss from Syphilitic Blindness in the U.S. (calculated for 1938) *J Ven. Dis. I form* 20 91 1939.

private physicians. It must include research in treatment and diagnosis.

The task of syphilis control—bringing patient and doctor together as soon as possible—is simple in theory difficult in practice. It is a job which requires the co-operation of the health departments and private physicians. All levels of government have joined in a program to direct this co-operative attack on venereal disease.

NATIONAL PROGRAM FOR VENEREAL-DISEASE CONTROL

The national program for the control of venereal disease is based on federal legislation designed to assist state and local health authorities and private physicians in controlling syphilis as well as the other venereal diseases. Activities are shared by all three levels of government. The federal government, through the United States Public Health Service, handles much of the research. It assists the states and local governments through financial grants-in-aid, medical consultants and other trained personnel, professional and public education and demonstrations of control methods. The actual job of diagnosis and treatment is in the hands of the state and local governments and private physicians.

This national program involves the total annual expenditure of almost $30,000,000 of public funds, slightly more than half of which is contributed by the federal government. In addition, many local governments have special venereal-disease programs financed out of their own treasuries and by private funds. More than half of the federal funds, or about $9,000 000 a year are divided among the states on the basis of population, financial need, and the extent of venereal disease. Another third of the federal money is assigned to states for special treatment centers the remainder is spent for research, demonstrations, education, training, administration, and supplies.

Extensive research activities are conducted by the Venereal Disease Division of the Public Health Service at its research laboratories and in co-operative studies with universities, foundations, and other agencies. These studies include antibiotics, biochemistry experimental syphilis, therapeutics, and other medical aspects of syphilis. Research in syphilis case finding methods also is conducted by the Public Health Service in co-operation with various state and local health departments.

Consultation service on many aspects of syphilis control is provided to the states through the administrative headquarters staff and personnel

of the Venereal Disease division stationed in the district offices of the United States Public Health Service. Direct assistance also is provided by specially trained medical officers, public health nurses, and administrative specialists who are assigned to work in areas of particular need under the supervision of the local health officers.

State and local governments, in their front-line battle against venereal disease, are concerned particularly with case finding, which is the basis of control, and with operation of diagnostic and treatment facilities. To this end, approximately 3 000 local out patient clinics and 60 rapid treatment centers for diagnosis and treatment are maintained by state and local health departments throughout the United States. Health departments also have laboratories for help in diagnosis and case management, educators for programs of public information, contact investigators for locating hidden cases, and divers other facilities and personnel in their fight against syphilis.

During 1947 local health departments used this machinery to examine almost 2 000 000 persons for venereal disease. Of this group, about 110 000 were found to have previously undiagnosed early syphilis, and about 50 000 were diagnosed as having late stages of the disease. About 142,000 cases of syphilis were admitted to public in-patient care facilities for syphilis treatment. Of these cases, 60 per cent were referred by local public clinics as cases without prior treatment. Others were cases that had previously received inadequate out patient treatment. Many were referred by private physicians, and others went to the rapid treatment centers on their own initiative.

SYPHILIS LEGISLATION

The national syphilis control program is based not only on federal legislation but also on state and local laws enacted in recognition of the public health aspects of syphilis and other venereal diseases. While these state laws vary they generally include

1. Morbidity reporting laws, requiring all cases of venereal disease to be reported to some central agency
2. Provisions for compulsory examination of persons suspected of having syphilis
3. Provisions for compulsory examination of couples prior to marriage, and of pregnant women
4. Requirements for testing applicants for certain occupations

5. Provisions for isolation of infectious venereal-disease cases, or safeguarding them during treatment to prevent infection of others
6. Prohibitions against advertising cures, treatment by other than licensed physicians, or the sale of remedies without prescriptions from registered physicians

Morbidity reporting of venereal diseases is fundamental in the control of syphilis. It is designed to provide state health officials with information on which to base their control activities. Morbidity reports not only provide a system for assuring proper care of the individual but also provide the basis for directing the activities and measuring the accomplishment of the syphilis control program.

The laws in many states require that persons reasonably suspected of being exposed to a venereal disease accept examination so that, if infected, they may be placed under treatment for the protection of others.

Many states also have premarital and prenatal blood-testing laws. The premarital laws established in 37 of the 48 states provide for the blood testing or clinical examination, or both, of persons contemplating marriage. Examination for syphilis at this time acts to reduce the transmission of syphilis in marriage and can serve as an occasion for giving sound venereal-disease educational information. The premarital laws, coupled with required serologic testing for syphilis of pregnant women in 30 states, acts as a guard against the transmission of syphilis to the unborn child.

Some areas require the testing of individuals prior to their employment in certain occupations. A very important part of any required syphilis testing program, aside from the discovery of cases, is the education of the public about syphilis.

One state, Alabama, has a law that "all persons between the ages of 14 and 50 residing or living in the State of Alabama shall have their blood examined for syphilis."

The laws in most states require that persons infected with syphilis in a communicable stage accept treatment, which is provided at public expense for those unable to afford payment to private physicians. If treatment is not accepted by persons in the infectious stage of syphilis, they may be removed by the State Board of Health to a hospital or other facilities for treatment, or for isolation until, in the opinion of the health officer they are no longer infectious.

If persons with infectious syphilis fail to continue with the authorized

course of treatment, or conduct themselves in a manner which will expose other persons to the disease, they may upon the complaint of the physician be investigated by the health department and committed to a hospital or institution if necessary

Most state public health laws prohibit the treatment of syphilis by other than licensed physicians and prohibit the publication of advertisements for the treatment of venereal diseases. They also prohibit the sale of drugs, medicines, or remedies for the treatment of syphilis except upon prescription of a physician.

Generally speaking, it is not considered necessary or advisable to use laws as a means for carrying out control measures unless infectious individuals refuse to co-operate. The legal implications, the fines, and penalties lie in the background of well-reasoned, established practices commonly accepted as workable schemes for obtaining voluntary co-operation in syphilis control.

CASE FINDING PROCEDURES

All efforts to control syphilis depend of course, upon finding individuals who have the disease so they can be treated. The remarkable recent developments of syphilotherapy are of no avail unless they can be applied to those who need treatment.

Three major methods are used to find syphilis cases. They include (1) contact investigation, which means tracing the disease from one person who has it to others with whom he has had intimate contact (2) public education of special groups or the general public and (3) screening or routine examinations, under which groups of people are examined regardless of whether or not they are suspected of having syphilis. Each method has special usefulness, but successful control of syphilis generally involves the use of all three.

Contact investigations.—Under the term contact investigation are included all the activities involved in the process of (1) obtaining from each infectious case of syphilis the names or other identification of all possible sources of the infection and all individuals who might have been infected by the patient prior to treatment, and (2) finding these persons and inducing them to undergo examination and, if necessary treatment.

Theoretically the investigation of persons known to have been sexual partners of a syphilitic individual during the period of his infectiousness and possible incubation period offers the most direct and profitable of all case finding techniques. But in practice there are disadvantages as

well as advantages in this method, although it has special potentialities which cannot be realized through the other techniques.

The difficulties in contact investigation arise from several sources. First there is the nature of the disease itself, involving as it does highly confidential social relationships. Then there is the added difficulty of finding personnel with sufficient skill and understanding to persuade the patient to talk about his contact. With regard to the latter there is not only the problem of dealing with the reluctance of the infected person, there is also the need for skill in eliciting half forgotten information from the patient which may provide the clue leading to a successful search for others with the disease.

It has long been recognized that the area where the least efficient contact investigation work has been done was among the contacts of patients under treatment in private practice. This constitutes a very promising field for intensive case finding

The private physician is in a most strategic spot to assist in this epidemiologic attack on syphilis. In the patient physician relationship, that rapport which the health department interviewer must struggle to attain is usually established easily A frank statement of the problem by the physician, with a request for the patient's co-operation, should result in a satisfactory contact interview This is not to minimize the problem, but it is believed that the success achieved by health-department clinics can be duplicated or bettered in the office of the private physician

The process of contact investigation is not, of course, completed with the naming of contacts by the infected person. These contacts must be located, examined, and placed under treatment if that proves to be necessary The human memory being what it is, and the population of this country being as mobile as it is, not all contacts are located. A good health department, with intensive effort, can usually locate between 60 and 70 per cent of the contacts reported to it for investigation.

The problem of locating and examining contacts is one which calls for the closest co-operation between the private physician and the local health department. The patient himself may be able to arrange for the examination of some of his contacts. The private physician may be able to arrange to get in touch with other contacts for the necessary physical examination. But there will always be certain instances, such as contacts out of the physician's immediate community or so poorly identified that investigation through such places as bars and taverns may be necessary in which the services of the health department are essential in locating the contact. Such services are always available to the physician. A telephone

call or a written report to the health department will result in a careful and discreet investigation.

There will, of course, be a continuing interest in the techniques and methods of contact interviewing and locating And although local needs and conditions must determine the methods used, one of the greatest present needs is practicable procedures by which the experience of one locality in the use of a particular method will be made available to other areas. In this way the expensive process of trial and error in separate localities may be avoided. Improvements in contact investigation will, perforce, be slow and gradual, and as efficiency increases it will become ever more difficult to show new gains. But the point of diminishing returns has certainly not yet been reached, and every possible means of improvement must still be explored.

Public education.—Public education, the second of the three methods of case finding is a broad term which covers several kinds of activity It includes the planned use of mass informational media such as daily newspapers, radio broadcasts, leaflets, motion pictures, posters, and exhibits for providing the general population or large special groups with facts about syphilis. Discussion meetings, speeches before small groups, conferences, and similar devices for reaching smaller selected groups are also commonly used.

Aggressive public education programs have long been used by local state, and national health agencies to promote many of the objectives of venereal-disease control. Formerly information leading to improved case finding was merely part of a larger program designed to inform the public on such matters as case holding, legislation, appropriations, social hygiene, and similar topics. It is only in recent years that the techniques and media of mass publicity have been used deliberately and specifically for promoting syphilis case finding This special use has taken two major directions (1) publicity designed to inform the public about case finding projects and to motivate individuals to co-operate in screen examinations and (2) publicity to acquaint large numbers of individuals with the symptoms of venereal disease, mode of transmission dangers when untreated, and the procedure to follow in obtaining diagnosis and treatment.

In the United States the first large-scale use of publicity to induce people to procure blood tests for syphilis was during World War I Following the war little was done until the thirties. In 1931 publicity for this purpose was used in connection with the Rosenwald demonstrations

which sought to determine the prevalence of syphilis among Negroes in five southern rural counties.

Intensive publicity campaigns urging the people to get blood tests were conducted by the Chicago Health Department in 1936 and 1939. During World War II numerous local informational programs, which included appeals for voluntary submission to blood tests, were conducted by local health departments with state and federal assistance.

In 1945 the New Orleans Board of Health with active participation by state and federal governments, conducted a public information campaign of short duration and great intensity the major purpose of which was to encourage persons with symptoms of gonorrhea to seek diagnosis and penicillin treatment from private physicians or public clinics. During the 45-day campaign approximately 4 000 cases of gonorrhea were found and treated. This number was more than would have been reported in that city during 2 years under normal operating conditions. The New Orleans publicity drive has been followed by similar intensive, effective public educational campaigns in many cities and counties in all parts of the country.

Screening examinations.—The third method of locating syphilis cases is the use of screening examinations by which large groups of people are examined for syphilis regardless of whether or not the disease is suspected in any of them. In some states, for instance, all pregnant women are required by law to have such examinations in many states premarital examinations are required and examinations are sometimes required as a condition to employment, or on admission to hospitals.

One of the most successful screening devices has been in connection with the educational programs described above, where whole communities were encouraged to undergo examination for venereal disease.

The earliest groups subjected to screen examinations were persons being admitted to hospitals, industrial workers, and certain categories of domestic or service workers. Other outstanding examples of screen examination are the blood tests required of Selective Service registrants prior to induction, and the legally required testing of an entire population within certain age groups as currently required in Alabama.

The screening examination as a syphilis case-finding technique to prevent the spread of syphilis has received considerable criticism. In areas having a low-prevalence rate, great numbers of individuals must be examined in order to find a relatively small number of infectious cases. Even in high-prevalence groups, the percentage of early cases found,

especially those in the open-lesion stage, has been relatively low The majority of infections found by this method have already reached the latent or late stages many of them are already known to the health authorities, and many have already received treatment. Also, it has been claimed that the examination gives individuals a false sense of security as they might become infected after examination and do nothing about it.

The difficulties and cost of screening examinations in finding cases of primary and secondary syphilis might seem to render this method undesirable for public health application. However consideration of all the purposes of case finding by whatever method, discloses the value of this technique. It must not be forgotten that, even after syphilis has become latent, it may occasionally be infectious and is thus of potential danger as a source of infection to others. Since the fetus may be infected, regardless of the stage of syphilis in the mother screening examinations which discover syphilis in pregnant women are very valuable. And even the discovery of late latent cases is worth while in that treatment will usually prevent the late crippling effects of syphilis.

EVALUATION OF CASE-FINDING TECHNIQUES

It would perhaps be appropriate to end this discussion of case finding with an analysis of the methods described. In a group of clinics where tabulations on "reason for coming to the clinic" are available, approximately two-thirds of the primary and secondary cases diagnosed came to the clinics of their own accord." Contact investigation accounted for approximately one-quarter of the cases, and the remaining cases came in because of screen testing court cases, and the like.

The distribution of cases brought in by the three methods reflects varying rates of total and early syphilis prevalence, differing degrees of receptiveness to education in the infected population and varying emphasis on each of the three methods, as well as the relative efficiency of the three techniques. While present evaluations of the respective merits of the different methods of case finding do not indicate what the distribution of emphasis should be in relation to local conditions and needs, it is felt that none of these methods, used singly gives maximum efficiency in any area.

Of more concern to the health officer than the cases coming in for specific reasons are the thousands of cases of acquired syphilis which are not diagnosed and treated while in the early infectious stages. It is estimated that during the period from July 1947 through June, 1948,

at least 185 000 cases of syphilis were acquired by civilians in continental United States. If the "reason for coming to the clinic" could be generalized for the entire country the following assumptions might be made regarding the fate of all early syphilis cases acquired during the year ending in June, 1948

	Number	Per cent
Cases of syphilis acquired	185,000	100.0
Early syphilis not in open lesion stage	99,000	53.6
Came to treatment in open-lesion stage	86,000	46 4
—because of own initiative	55,200	29.8
—because of contact investigation	20,600	11 1
—for other reasons	10,200	5 5

Thus, at best, approximately 30 per cent of acquired cases came to diagnosis of their own accord during the primary and secondary stage, 11 per cent came because of contact investigation, and at least 54 per cent failed to be diagnosed during the open lesion stage. This failure to diagnose early syphilis at the earliest possible time is the challenge of syphilis control. Facilities, drugs, and the knowledge to diagnose and treat syphilis are available, but not enough early cases are being found and treated. Is more intensive contact investigation the answer or should more time and effort be given to public information? Probably health officers and private physicians will continue to use all of the weapons at their command. Recent improvements in contact-investigation techniques and research into the blocks and resistances which keep infected persons from coming to diagnosis hold promise. Improvement of educational methods offers hope that an ever increasing proportion of cases may come to treatment voluntarily in the early stages. The proportion of cases reported in the primary and secondary stages is increasing continuously All this is encouraging because, if the problem of improved case finding is not solved, substantially better control of the disease cannot be expected.

CASE HOLDING

The modern penicillin treatment of syphilis which can be completed in a short period has largely eliminated the old problem of case holding. In the days when treatment required regular weekly visits to a physician for 18 months, one of the major problems was to keep the patient under continuous treatment. Less than 30 per cent of those admitted to clinics

completed minimum protective treatment. Health department investigators had to spend a major part of their time tracing lapsed patients and bringing them back to treatment.

With modern therapy a different, though less time-consuming problem of case holding exists. Although it is no longer a major difficulty to complete the treatment of patients, it is necessary to have them return at regular intervals for posttreatment observation to guard against relapses. Thus, the follow up of treated patients now becomes an important phase of the public health control effort.

Methods of case holding —The first requirement in the follow-up of treated patients is to obtain their intelligent co-operation. Unless patients understand something about the nature of their disease, the possibility of relapse and reinfection, and the importance of repeated examinations, intelligent co-operation cannot be expected. Furthermore, patients must feel that the physicians and clinic personnel are definitely interested in their welfare. The attitude of clinic staffs—physicians, nurses, clerks, and investigators—is of the greatest importance in case holding All personnel engaged in the control of syphilis should be free from prejudice regarding the disease yet they must understand the sense of guilt and many misconceptions which others may have about venereal infections. In all cases the patient must be sure that information given to the interviewer will be treated confidentially Only those who approach syphilis in a matter-of fact way without sentimentality or censure, can put infected individuals at ease, gain their attention, and obtain as well as give essential information. Even the most ignorant patient welcomes instruction that is couched in understandable language and that is given to help the individual and not merely for the sake of the clinic record.

Elaborate social case histories are less important in case holding than giving proper instruction about the disease and obtaining specific information which will make it possible to locate the patient in the future. At the time of the original interview all pertinent facts which will later aid in the follow-up of the patient should be recorded, such as names and addresses of relatives or friends, referring agencies, place of employment, names and addresses of unions, church and club, draft board, home relief social security number and criminal record.

Various methods have been used to persuade delinquent patients to return for follow-up examinations. Form letters are the cheapest and easiest procedure, but in some cases registered letters or telegrams will produce results not obtainable by form letters. Personal visits to the homes of delinquent patients are costly but may be needed, especially when

REPORTED SYPHILIS DEATH RATES PER 100,000 POPULATION
UNITED STATES, 1933 1946, AND ESTIMATE FOR 1947

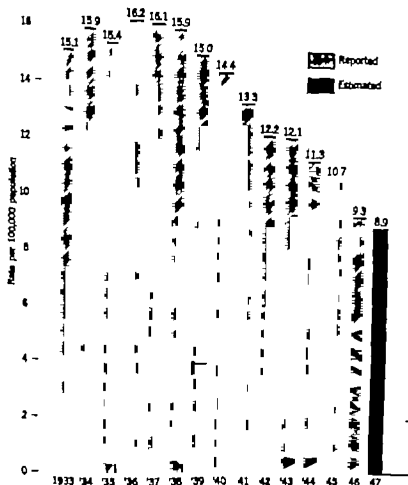


FIG. 67 Reported syphilis mortality has decreased for 11 consecutive years. Source, N tional Office of Vital Statistics

1933–43 Vital Statistics, Special R ports, Vol. 22, No. 1 February 28, 1945
1944–45 Vital Statistics, Special Reports, Vol. 27 No. 2, May 16, 1947
1946 Communication on final tabulations
1947 Estim ted 10 per cent sample of 1947 reports, Current Mortality Analysis, December 1947

patients are found to have relapsed and have failed to return for treat ment.

PROGRESS IN CONTROL OF SYPHILIS

There is a definite downward trend in syphilitic deaths, mental hospital admissions because of syphilis, and the number of children born with congenital syphilis. Fig 67 shows the trend. Syphilis mortality has decreased from 15 1 per 100 000 in 1933 to an estimated 8.9 in 1947 For each year since 1936 there has been a reduction in the mortality rate. Infant mortality as a result of syphilis was down one-third from the 1936 figure.

It will be noted in Fig 68 that, in spite of the war and heavy Selective Service blood testing there has been a gradual decline in the total syphilis cases reported since 1943 The reports of late cases of syphilis decreased from 1943 to 1947 with a slight increase for 1948 On the other hand, cases of early syphilis increased during the years of the war and immediately after the war Some of the increase in early syphilis from 1943 to 1947 was probably due to improved case finding and especially case finding in the Armed Forces, which was almost completely effective.

Primary and secondary syphilis for civilians as reported by quarters for the fiscal years 1947–48 shows a steady decline. From the first quarter of the fiscal year 1947 to the third quarter of the fiscal year 1948 the figures were 28,866 27 173 26 271 24,284 22,348 20 697 and 19,518 There is no reason to believe that there has been any decrease in case finding effectiveness during this period nor any decrease in reporting quality We may well be seeing the beginning of a pronounced down ward trend in the incidence of syphilis.

Apart from estimates of trends in syphilis, morbidity reporting is also useful in determining the geographic location of syphilis cases. Annual reported syphilis case rates calculated for individual states show a varia tion from 66 per 1 000 for North Dakota in 1947 to 8.62 per 1 000 for Mississippi in the same year Morbidity data by sex and color indicate reported case rates are approximately equal for males and females but about 12 times as high for nonwhites as for whites. Morbidity reports also indicate the proportion of cases diagnosed by private physicians as compared with public clinics. Approximately two-thirds of reported syphilis cases in the United States are reported by health departments and clinics and the remainder by private physicians.

The figures indicate that the intensified syphilis control program of

FIG. 62. TREND OF SYPHILIS MORBIDITY REPORTING, UNITED STATES CIVILIAN AND ARMED FORCES, 1941–48

FISCAL YEAR	ESTIMATED POPULATION IN THOUSANDS	Reported cases: TOTAL, INCLUDING STAGE NOT STATED	Reported cases: PRIMARY OR SECONDARY	Reported cases: ALL EARLY SYPHILIS (PRIMARY SECONDARY EARLY LATENT)	Reported cases: CONGENITAL	Reported cases: LATE AND LATE LATENT	Rate per 1 000 population: TOTAL, INCLUDING STAGE NOT STATED	Rate per 1 000 population: PRIMARY OR SECONDARY	Rate per 1 000 population: ALL EARLY SYPHILIS (PRIMARY SECONDARY EARLY LATENT)	Rate per 1 000 population: CONGENITAL	Rate per 1 000 population: LATE AND LATE LATENT
Continental United States civilians											
1941	131 897	477,841	67 958	176,616	17,592	201 190	3 623	0.515	1.339	0.133	1 525
1942	131 943	472,245	75,704	192,137	16 924	202,216	3.579	.574	1 456	128	1.533
1943	128,728	364 918	82,230	231 139	16,173	252,995	4.388	639	1 796	126	1 965
1944	127 028	458,199	78,418	200,808	13,576	203,396	3 607	617	1.581	107	1.601
1945	127,037	356,315	77 007	178,142	12,339	142,731	2.805	.606	1 402	097	1 124
1946	133,543	360,918	94 957	202,293	12,106	125,836	2.703	711	1.515	.091	942
1947	140,974	373,296	106,594	214 349	12,284	122,257	2.648	756	1.520	.087	.867
1948 est.	143,500	341 000	82,000	180 000	13 000	125,000	2.376	.571	1 254	.091	.871
Total civilian and armed forces											
1941	132,638	484 647	74 764	183,422	17,592	201 190	3 654	0.564	1.383	0.133	1 517
1942	133,953	486,386	89 845	206,278	16 924	202,216	3.631	671	1 540	126	1.510
1943	135,646	594 021	111,333	260,242	16,173	252,995	4.379	.821	1 919	119	1.865
1944	137,368	501 947	122,166	244 556	13,576	203,396	3.654	889	1 780	.099	1 481
1945	138,923	411 840	132,532	23_,667	12,339	142,731	2 965	954	1 682	089	1 027
1946	140,387	409,531	143 570	250,906	12,106	125 836	2.917	1 023	1 787	086	896
1947	142,673	399 067	132,365	240,120	12,284	122,257	2.797	928	1 683	086	.857
1948 est.	145 000	357,000	98,000	196,000	13,000	125,000	2.462	676	1.352	090	.862

As of January 1 (mid-point of fiscal year).

Source: Civilian Morbidity U.S. Public Health Service, Form 8958-B. Army Morbidity: U.S. Army. Navy Morbidity: Statistics of Navy Medicine (provisional data). Population, Bureau of the Census, P-46, No. 6

recent years is beginning to show results. With the better treatment methods now available, the improvement within the next few years should be more marked. But the success of the program depends upon constant application of all the best techniques for getting individuals with the disease into doctors' offices, and into the clinics where they can be treated before they infect others.

Bringing all those with the disease to early treatment depends on the continued interest and co-operation of the public—continued determination of the people to fight syphilis relentlessly unremittingly until the last case has been found and treated. Success depends on the skill, the courage, the hard work, and the faith of the physician in private practice, and in the health department, of the nurse, the health educator the contact investigator and all the others in a disciplined army of men and women who are devoting part or all of their professional careers to the fight against syphilis.

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